Faculty of Science

Department of Chemistry

Molecular Design & Synthesis

University of Leuven (KU Leuven)

Synthesis and post-transformations of propiolic acid-derived Ugi adducts

Promoter

Prof. Dr. Erik Van der Eycken

Doctoral Thesis

Anatoly A. Peshkov

August 2015

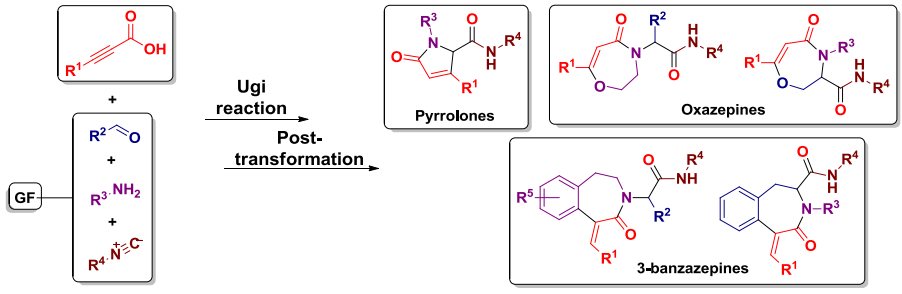
Members of the jury

Prof. Dr. Wim Dehaen
Prof. Dr. Guy Koekelberghs,
Prof. Dr. Arthur Van Aerschot
Prof. Dr. Johan Van der Eycken
Prof. Dr. Kourosch Abbaspour Tehrani
Prof. Dr. Erik Van der Eycken (Promoter)

Preface

Development of novel synthetic methodologies towards heterocyclic molecules is of exceptional importance in a view of their potential applications in medicinal chemistry. A recent success in the use of multi-component reaction as well as a fast rise of a diversity-oriented synthesis (DOS) concept prompted us to start work in this direction.

Our group has a long-standing interest in the Ugi reaction chemistry and in the triple bond functionalizations. Getting inspiration from there, we decided to put an emphasis on the application of 3-substituted propiolic acids in a four-component Ugi reaction anticipating that the triple bond of propiolic acid in combination with other functionalities would allow to subject the resulting Ugi adducts to a large variety of post-transformations. This resulted in the development of several practical methodologies providing a diversity-oriented access towards a number of interesting heterocyclic scaffolds such as pyrrolones, oxazepines and 3-benzazepines.



Acknowledgment

First, I would like to express my sincere gratitude to my supervisor, Prof. Dr. Erik V. Van der Eycken, for his continuous support and guidance as well as for giving me an opportunity to start research in the area of synthetic methodology despite my chemical engineer background.

I am thoroughly grateful to the members of my examination committee Prof. Dr. Wim Dehaen, Prof. Dr. Guy Koekelberghs, Prof. Dr. Arthur Van Aerschot, Prof. Dr. Johan Van der Eycken, Prof. Dr. Kourosch Abbaspour Tehrani for invaluable comments and suggestions while evaluating my thesis.

I would like to thank Mr. Karel Duerinckx for his help and assistance with NMR spectroscopy.

Thanks are also given to Ing. Bert Demarsin, Mr. Jan Goeman and Prof. Jef. Rozenski for their kind help with High Resolution Mass Spectra (HRMS).

I owe particular thanks to my brother, Dr. Vsevolod Peshkov, for his assistance and support throughout these years.

Also I want to thank Olga P. Pereshivko, Tran Thi Thu Trang, and Anton A. Nechaev for their collaboration and help.

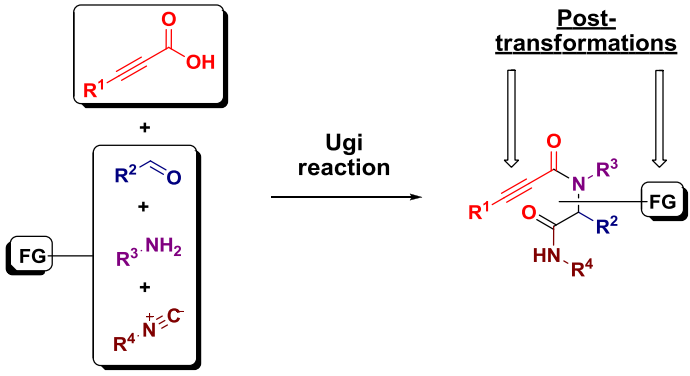
I am deeply grateful to all my colleagues from Molecular Design & Synthesis for creating a professional and encouraging working atmosphere.

I want to thank my mother, my family and my friends for their love and support.

Finally, I would like to acknowledge the financial support provided by Erasmus Mundus External Cooperation Window (Triple I - Integration, Interaction and Institutions).

Summary

The research described in this thesis centers on the application of 3-substituted propiolic acids in a four-component Ugi reaction. The triple bond of propiolic acid in combination with other functionalities produces an important type of Ugi adducts which could be then readily applied in a large variety of post-transformations providing a diversity-oriented access towards a large number of heterocyclic scaffolds (Scheme 1).



Scheme 1. General concept

Chapter 1 serves as an introduction into the post-Ugi chemistry in general, and into the reactivity of Ugi-adducts bearing C-C triple bond in particular. The objectives and targets of the current research are also formulated in this chapter.

Chapter 2 is dedicated to the elaboration of a novel cascade transformation involving Ugi reaction followed by enolization-triggered 5-*endo-dig* carbocyclization and retro-Claisen fragmentation providing an efficient and fast access to 1*H*-pyrrol-2(5*H*)-one core.

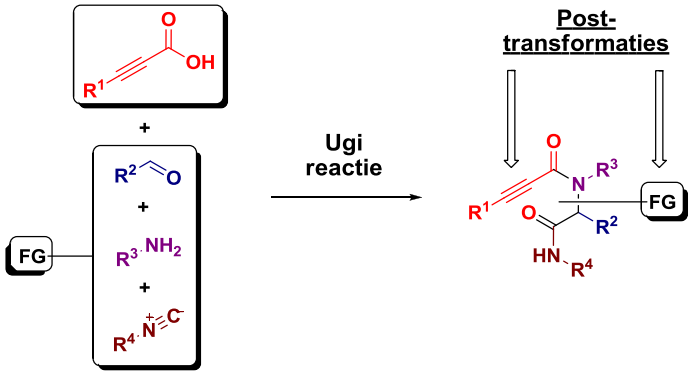
Chapter 3 describes a comprehensive study on gold- and silver-catalyzed cycloisomerizations of hydroxypropargylamides into oxazepines. Three different types of hydroxypropargylamide substrates derived from either amide coupling or Ugi reaction have been validated providing selective and general access to a medium-ring oxazepine core.

Chapter 4 deals with a two-step sequence involving Ugi reaction followed by reductive Heck cyclization leading to a 3-benzazepine framework. Several aspects related to the substrate scope and the optimal distribution of the required functional groups have been addressed, resulting in a diversity-oriented synthesis of a small library of title compounds, featuring four distinct types of substitution pattern.

Finally, **General conclusions and future perspectives** are outlined.

Samenvatting

Het onderzoek dat in deze thesis beschreven wordt, handelt over de toepassing van 3-gesubstitueerde propiolzuren in een vier-component Ugi reactie. De drievoudige binding van dit propiolzuur, in combinatie met andere functionaliteiten, resulteert in de vorming van een belangrijk type van Ugi-adduct dat kan gebruikt worden in een grote variëteit van op diversiteit-georiënteerde post-transformaties, die toegang geven tot een groot aantal heterocyclische skeletten (Schema 1).



Schema 1. Algemeen concept.

Hoofdstuk 1:

Inleiding tot post-Ugi transformaties in het algemeen, en tot de reactiviteit van Ugi-adducten, welke een C-C drievoudige dragen, in het bijzonder. De specifieke doelen en objectieven van dit onderzoek

worden eveneens geformuleerd en bekommentarieerd in dit hoofdstuk.

Hoofdstuk 2:

Op punt stellen van een nieuwe cascadereactie waarbij een Ugi-reactie betrokken is, gevolgd door een enolisatie-gestuurde 5-*endo*-*dig* carbocyclisatie en retro-Claisen-fragmentatie, resulterend in de efficiënte en snelle vorming van het 1*H*-pyrrol-2(5*H*)-on-skelet.

Hoofdstuk 3:

Studie van goud- en zilver-gekatalyseerde cycloïsomerisaties van hydroxypropargylamides leidend tot oxazepines. Drie verschillende types van hydroxypropargylamidesubstraten – gesynthetiseerd via amidekoppeling of via Ugi-reactie - worden onderzocht voor de selectieve synthese van oxazepines van medium ringgrootte.

Hoofdstuk 4:

Twee-stapsreactie van een Ugi-reactie gevolgd door een reductieve Heck-cyclisatie, met vorming van een 3-benzazepineskelet. Verschillende aspecten betrekking hebbende op de variatie van het substraat en de optimale verdeling van de vereiste functionele groepen worden onderzocht, resulterend in een op diversiteit geöriënteerde synthese van een kleine bibliotheek van deze verbindingen, die vier verschillende types van substitutiepatroon vertonen.

Finaal besluit en toekomstperspectieven.

List of abbreviations

Ac	acyl
Alk	alkyl
Ar	aryl
Bn	benzyl
*n*Bu	butyl
*i*Bu	isobutyl
*t*Bu	tertiary butyl
CI	chemical ionization
Cy	cyclohexyl
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCC	*N*,*N'*-dicyclohexylcarbodiimide
DCE	1,2-dichloroethane
DMA	*N*,*N*-dimethylacetamide
DMF	*N*,*N*-dimethylformamide
DMSO	dimethyl sulfoxide
EI	electron ionization (formerly known as electron impact)
ESI	electrospray ionization
Et	ethyl
FG	functional group
HPLC	high-performance liquid chromatography (formerly referred to as high-pressure liquid chromatography)
HRMS	high-resolution mass spectra
MCR	multicomponent reaction

Me	methyl
Mes	mesityl
MSDS	material safety data sheet
MW	microwave or microwave irradiation
NMR	nuclear magnetic resonance
Ph	phenyl
PMB	*p*-methoxybenzyl
*n*Pr	propyl
rt	room temperature
OTf	trifluoromethanesulfonate, also known by the trivial name triflate
THF	tetrahydrofuran

Table of Contents

Reproduced in part with permission from

[Assembly of a 1H-Pyrrol-2(5H)-one Core through a Cascade Ugi Reaction/5-*endo*-*dig* Carbocyclization/Retro-Claisen Fragmentation Process, Anatoly A. Peshkov, Vsevolod A. Peshkov, Zhenghua Li, Olga P. Pereshivko, Erik V. Van der Eycken, *European Journal of Organic Chemistry*, **2014**, 6390–6393] Copyright © 2014, John Wiley and Sons.

[Gold- and Silver-Catalyzed 7-*endo*-*dig* Cyclizations for the Synthesis of Oxazepines, Anatoly A. Peshkov, Anton A. Nechaev, Olga P. Pereshivko, Jan L. Goeman, Johan Van der Eycken, Vsevolod A. Peshkov, Erik V. Van der Eycken, *European Journal of Organic Chemistry*, **2015**, 4190–4197] Copyright © 2015, John Wiley and Sons.

[Diversification of the 3-benzazepine scaffold applying Ugi/reductive Heck sequence, Anatoly A. Peshkov, Vsevolod A. Peshkov, Olga P. Pereshivko, Erik V. Van der Eycken, *Tetrahedron,* **2015***, 71,* 3863–3871] Copyright © 2015, Elsevier.

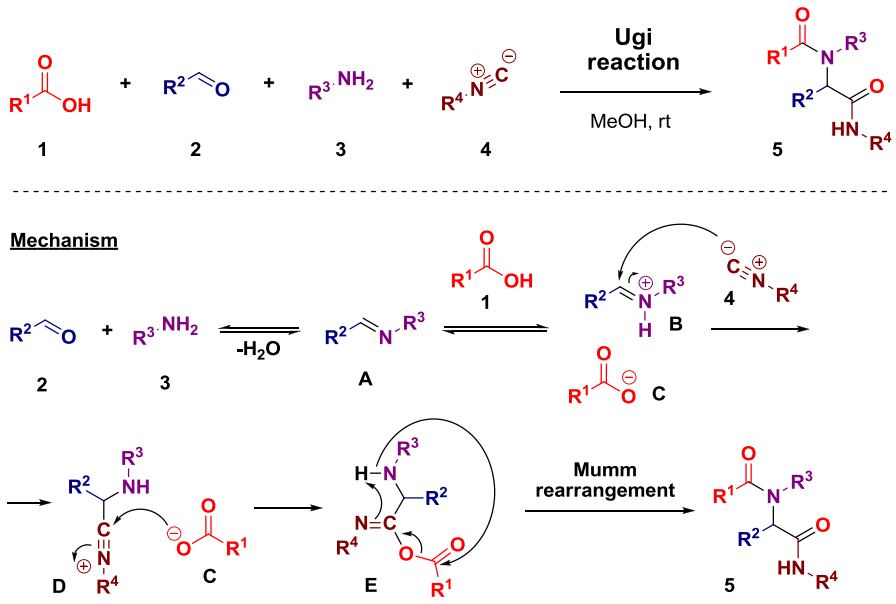
[Heck–Suzuki Tandem Reaction for the Synthesis of 3-Benzazepines, Anatoly A. Peshkov, Vsevolod A. Peshkov, Olga P. Pereshivko, Kristof Van Hecke, Rakesh Kumar, Erik V. Van der Eycken, *Journal of Organic Chemistry,* **2015***, 80*, 6598–6608] Copyright © 2015, American Chemical Society.

Chapter 1

1. Introduction and objectives of the work

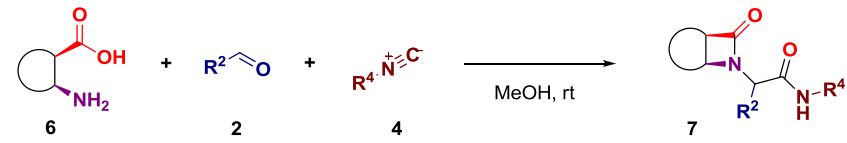
1.1. The Ugi reaction for the synthesis of heterocycles

Multicomponent reactions (MCRs) constitute one of the most powerful and attractive tools in synthetic organic chemistry allowing the generation of structurally complex and diverse products in a step- and atom-economic manner from rather simple and accessible precursors.[1] Since the first report by Ivar Ugi and co-workers,[2] the four-component Ugi reaction has been considered as one of the most versatile and robust MCRs.[3] The typical Ugi reaction utilizes a carboxylic acid **1**, an aldehyde (more rarely ketone) **2**, a primary amine **3** and an isocyanide **4**. The Ugi reaction is believed to start with a condensation of an aldehyde **2** and an amine **3** to form an imine **A** with a concomitant loss of one equivalent of water. Protonation by a carboxylic acid **1** leads to the formation of an activated iminium ion **B** that undergoes nucleophilic attack by an isocyanide **4**. The resulting intermediate **D** undergoes second nucleophilic addition with the carboxylic acid anion **C** to form **E**. The final step is a Mumm rearrangement[4] that transfers the R^1 acyl group from oxygen to amine-originated nitrogen to afford a final linear product **5** featuring a peptide backbone (Scheme 2).



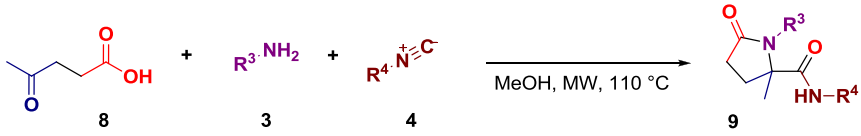
Scheme 2. The typical four-component Ugi reaction.

The possibilities to rigidify the Ugi adduct do exist. Thus, a considerable part of Ugi-based synthetic protocols, either directly or in combination with various post-transformations, aim for the diversity-oriented synthesis of heterocyclic scaffolds. The easiest way is to get the heterocyclic core directly via Ugi reaction by combining two of the required functionalities in one of the components. This approach is illustrated by a four-center three-component Ugi reaction elaborated by Fülöp and coworkers that utilizes alicyclic *β*-amino acids **6**, aldehydes **2**, and isocyanides **4** to obtain alicyclic *β*-lactams **7** (Scheme 3).[5]



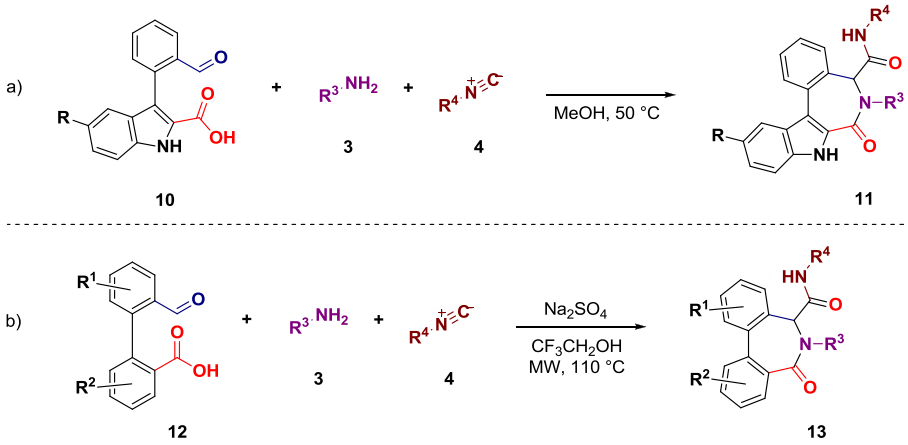
Scheme 3. Three-component Ugi reaction for the synthesis of alicyclic *β*-lactams **7**.

A similar idea was exploited by Tye and Whittaker in the microwave-assisted three-component Ugi reaction of levulinic acid **8** with various amines **3**, and isocyanides **4** for the preparation of γ-lactam derivatives **9** (Scheme 4).[6]



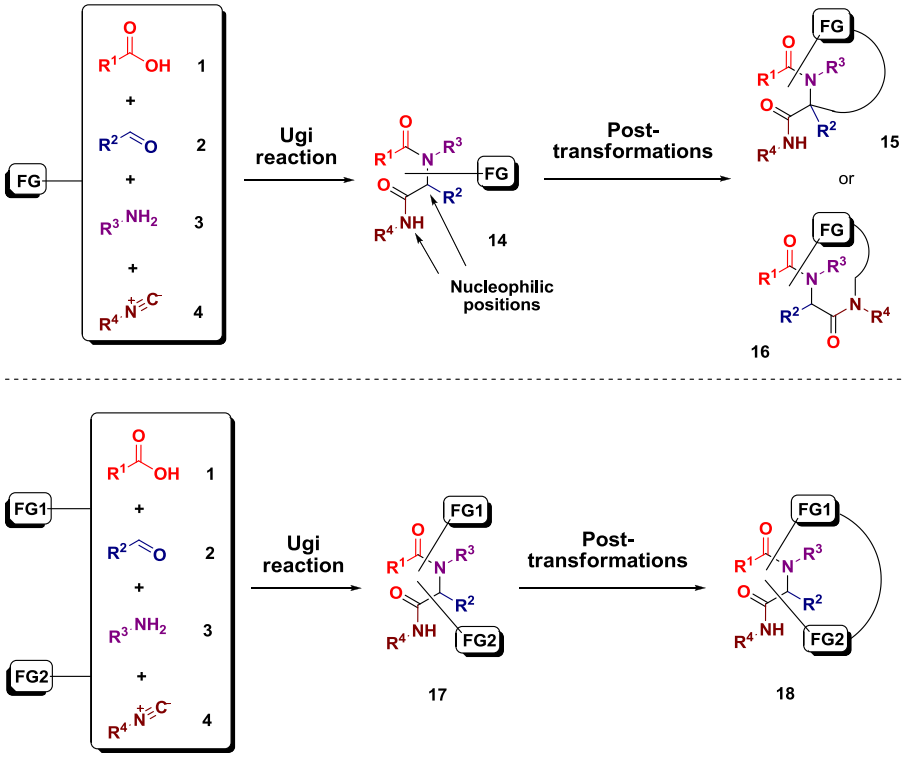
Scheme 4. Three-component Ugi reaction for the synthesis of γ-lactams **9**.

The carbonyl and acidic functionalities could also be linked through the biaryl moiety. The application of such substrates **10** and **12** in the Ugi reaction provided an efficient access to biologically relevant libraries of indolobenzazepinones **11** (Scheme 5a)[7] and dibenzoazepinones **13** (Scheme 5b).[8]



Scheme 5. Synthesis of seven-membered azepine frameworks **11** and **13** via three-component Ugi reaction.

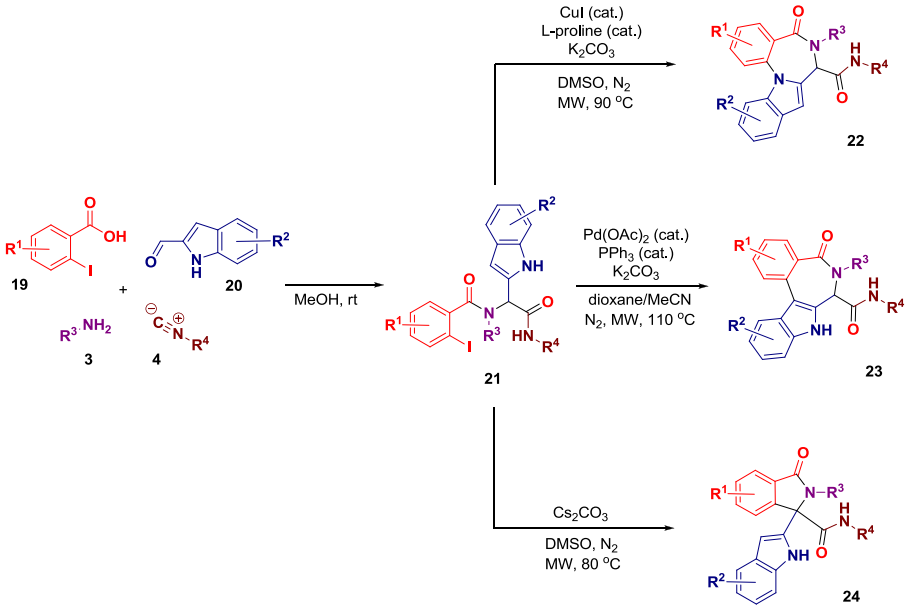
As can be seen from the above examples the direct strategy could be useful to access various types of heterocycles when combined with some basic elements of rational design. However, it still suffers from one major drawback, which is the limited number of possibilities that allow incorporating two Ugi-functionalities in one substrate. Thus, a more common way to attain heterocycles through the Ugi chemistry would be to use different post-transformations.[9,10] This is possible when the Ugi reaction is conducted with starting materials that bear one or two additional functional groups. The resulting Ugi-adducts **14** and **17** could be then subjected to further transformations, typically cyclizations, eventually yielding heterocyclic cores **15**, **16** and **18** (Scheme 6).



Scheme 6. Post- Ugi transformations leading to heterocycles.

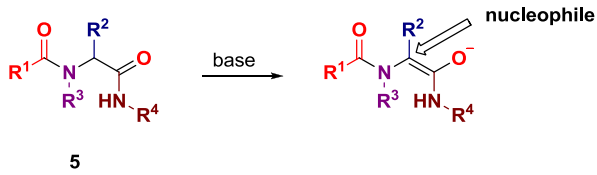
Furthermore, the power of the Ugi/post-transformation sequence could be reinforced when the same Ugi-adduct is converted into several different heterocyclic scaffolds. In 2013, Liu and co-workers described a rapid and selective access to three distinct sets of indole-based heterocycles **22-24** from a single set of Ugi-adducts **21** derived from 2-iodobenzoic acid **19** and indole-2-carbaldehyde **20** (Scheme 7).[11] When adducts **21** were subjected to copper catalysis in the presence of L-proline and K_2CO_3, N1-indole-arylation products **22** were preferentially formed. Remarkably, switching to palladium catalysis drove the reaction in the direction of C3-indole-arylation selec-

tively yielding product **23**. Finally, isoindolinone derivatives **24** were efficiently assembled through Cs_2CO_3-promoted carbocyclization of **21** that presumably proceeds through the nucleophilic aromatic substitution of aryliodide with the amide enolate.



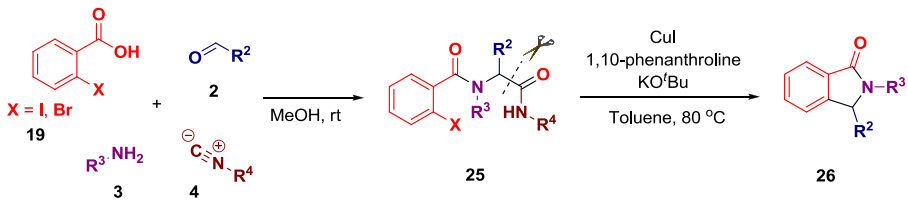
Scheme 7. Diverged access to three distinct sets of indole-containing heterocycles from a single set of Ugi-adducts.

Similarly to the last Liu process, a number of post-Ugi transformations directly employ the enolizable amide group (Scheme 8) as a convenient nucleophilic reactive site, which is by default present in a typical Ugi adduct **5**.



Scheme 8. Enolizable amide group in a typical Ugi adduct.

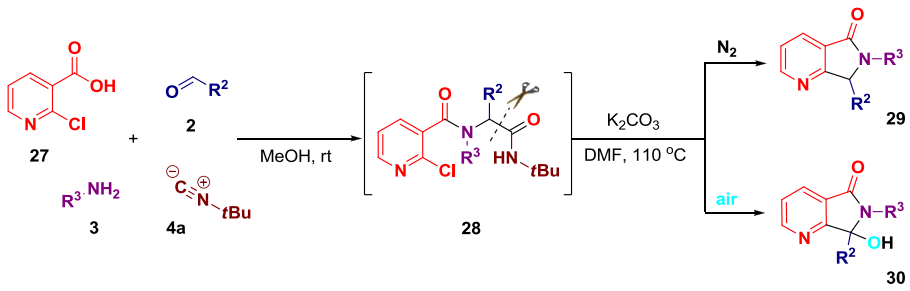
For example, Chauhan and co-workers disclosed an efficient route towards isoindolinones **26** *via* Ugi reaction followed by a Cu-catalyzed carbocyclization accompanied by a fragmentation process, leading to the loss of the isocyanide-originated amide moiety (Scheme 9).[12]



Scheme 9. Synthesis of isoindolinones **26**.

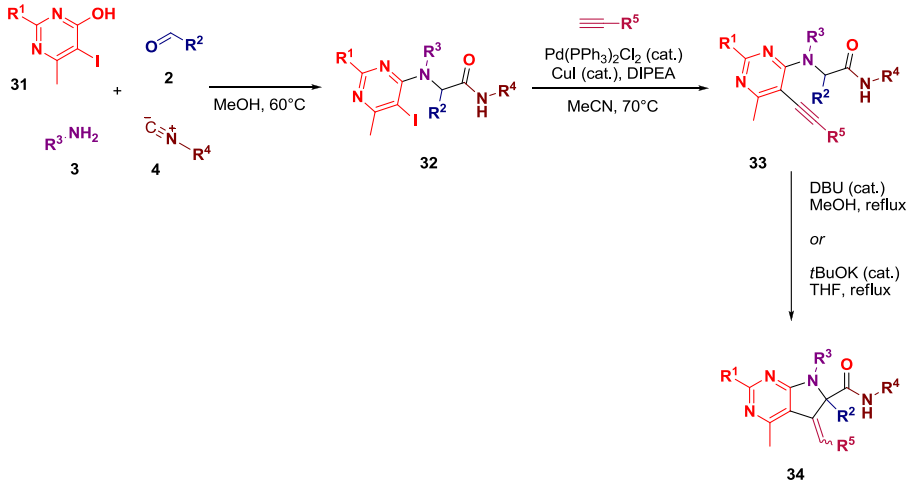
Based on Liu's and Chauhan's precedents, our group has evaluated this chemistry with 2-chloronicotinic acid-derived Ugi adducts **28** assuming that an electrophilic imidoyl chloride motif could be a suitable reaction partner for the nucleophilic amide enolate. It was found that such adducts **28** indeed undergo base-promoted cyclization with concomitant cleavage of the isocyanide-originated amide group similarly to Chauhan's process. Treatment of crude 2-chloronicotinic acid-derived Ugi adduct **28** with K_2CO_3 under inert atmosphere at 110 °C led to the formation of 6,7-dihydro-5*H*-pyrrolo[3,4-*b*]pyridin-5-one **29**, while analogous reaction performed under air atmosphere gives rise

to the formation of oxidized 7-hydroxy-6,7-dihydro-5*H*-pyrrolo[3,4-b]pyridin-5-one **30** (Scheme 10).[13]



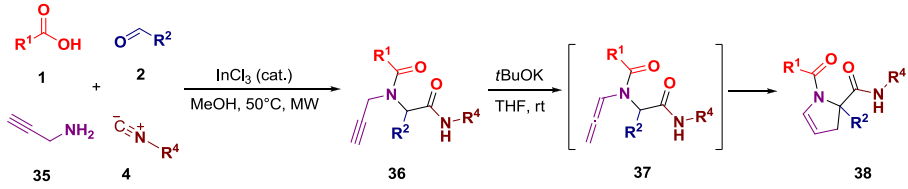
Scheme 10. Synthesis of 6,7-dihydro-5*H*-pyrrolo[3,4-*b*]pyridin-5-ones **29** and **30**.

Complimentary to the above processes, it has been demonstrated that the Ugi adducts bearing triple bond also readily undergo analogous amide enolization-driven cycloisomerizations. In 2010, El Kaïm, Grimaud and Wagschal described an efficient route towards highly substituted pyrrolo[2,3-*d*]pyrimidines **34** through an Ugi-Smiles/Sonogashira sequence, followed by base-catalyzed intramolecular cyclization (Scheme 11).[14]



Scheme 11. Synthesis of pyrrolo[2,3-*d*]pyrimidines **34**.

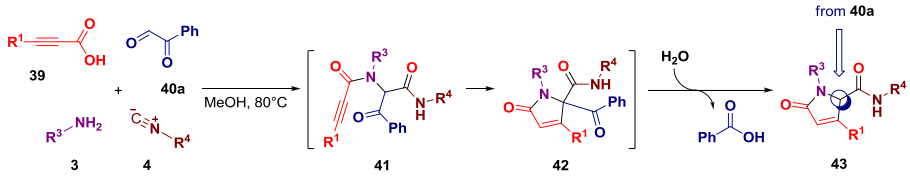
In 2012, Polindara-García and Miranda developed a *t*BuOK-promoted alkyne-allene isomerization of propargylamine-derived Ugi-adducts followed by enolization and cyclization into 2,3-dihydropyrroles **38** (Scheme 12).[15]



Scheme 12. Synthesis of 2,3-dihydropyrroles **38**.

We have reasoned that the application of 3-substituted propiolic acids **39** in combination with phenyl glyoxal **40a** [16,17] might provide an interesting extension to these methodologies, through the generation of Ugi adducts **41** (Scheme 13) that should be even more prone to

enolization-triggered cycloisomerizations due to the Michael-acceptor nature of a triple bond conjugated with an amide group and the presence of an additional electron-withdrawing group at the enolizable position. We were pleased to find that the proposed intermediates **41** spontaneously cyclize into pyrrolones **42** which subsequently undergo retro-Claisen fragmentation into the final pyrrolones **43**[18] through cleavage of the benzoyl moiety (Scheme 13).



Scheme 13. Synthesis of pyrrolones **43**.

A detailed study on the scope and limitation of this novel cascade transformation is outlined in the **Chapter 2**.[19]

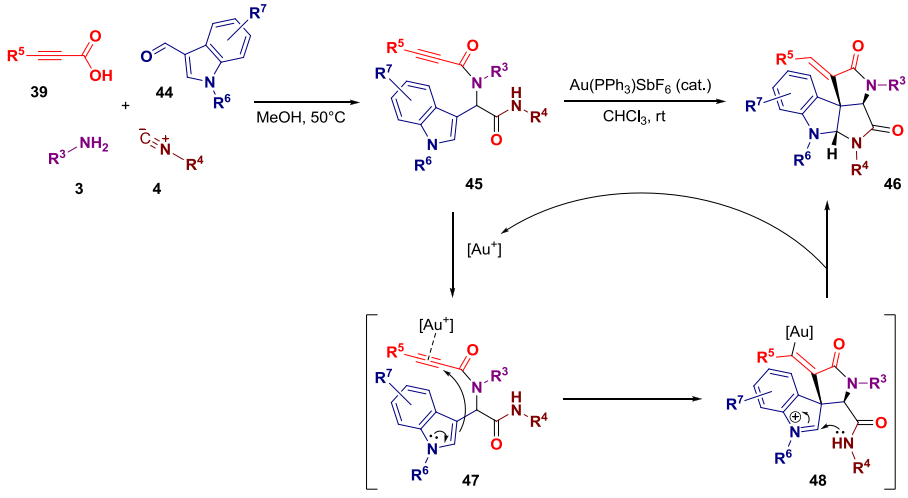
1.2. Merging the Ugi reaction and gold catalysis

The triple-bond activation by coinage metal salts towards intramolecular nucleophilic attack, resulting in hetero- or carbocyclization, has become one of the prevalent strategies in modern heterocyclic chemistry.[20] Such processes not only provide an efficient entry to many common heterocycles,[21] but also serve the goal of broadening the existing chemical space by leading to a large variety of hitherto unknown and structurally complex heterocyclic scaffolds[22] that could be of great interest for medicinal chemistry. Several of these procedures aim to synthesize medium-ring containing heterocycles[23] that

are of particular importance due to their large occurrence amongst natural and biologically active compounds.

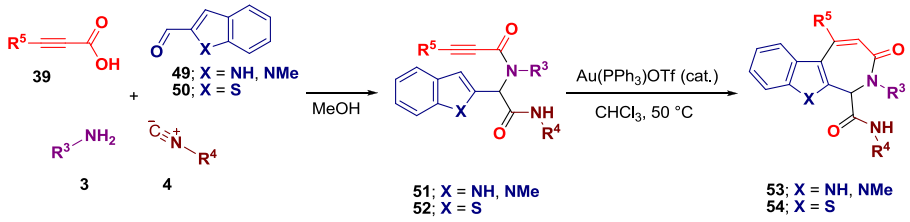
In this regard, our group has recently studied the application of 3-substituted propiolic acids **39** in the four-component Ugi reaction. The generated adducts, bearing a triple-bond functionality, were employed in a variety of gold-catalyzed post-Ugi transformations providing an access to a wide range of interesting heterocycles.

For example, our group has efficiently exploited the catalytic activity of cationic gold complexes in a diversity-oriented approach towards fused polycyclic spiroindolinones **46**.[24] This strategy combines 3-substituted propiolic acids **39** with indole-3-carbaldehydes **44** to generate the Ugi adducts **45** featuring a unique ‘‘branched-handed’’ architecture that subsequently undergo a cationic Au(I)-catalyzed diastereoselective domino cyclization process involving *exo-dig*[25] cyclization followed by intramolecular trapping of the resulting spiro intermediate **48** delivering the final product **46** (Scheme 14).[26]



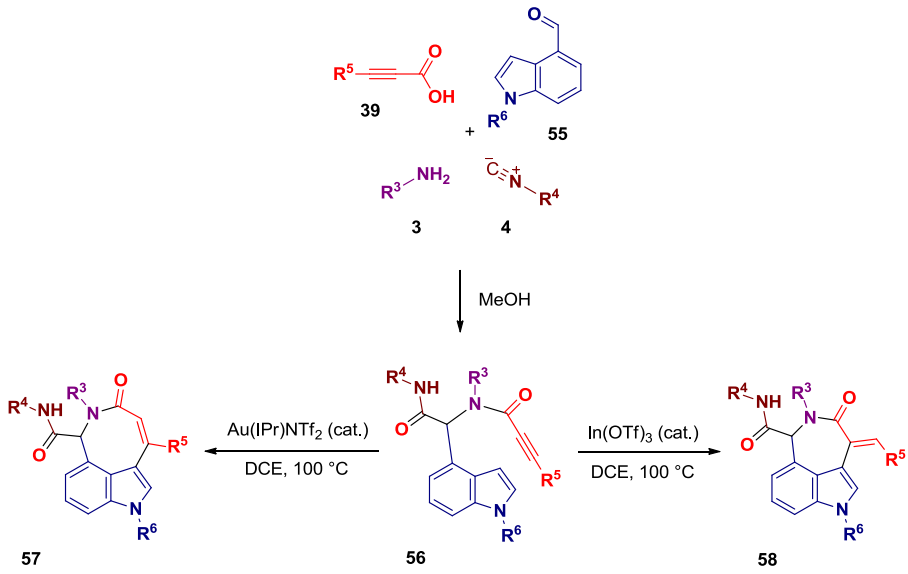
Scheme 14. Synthesis of polycyclic spiroindolinones **46**.

Interestingly, placing the carbonyl group in the 2-position of the indole core **49**, or employing benzo[b]thiophene-2-carbaldehyde **50**, gave rise to other types of Ugi adducts **51** and **52** that are prone to Au(PPh$_3$)OTf-catalyzed *endo-dig* cyclization, resulting in the formation of medium-ring containing azepinoindoles **53** and azepinobenzothiophenes **54** respectively (Scheme 15).[27]



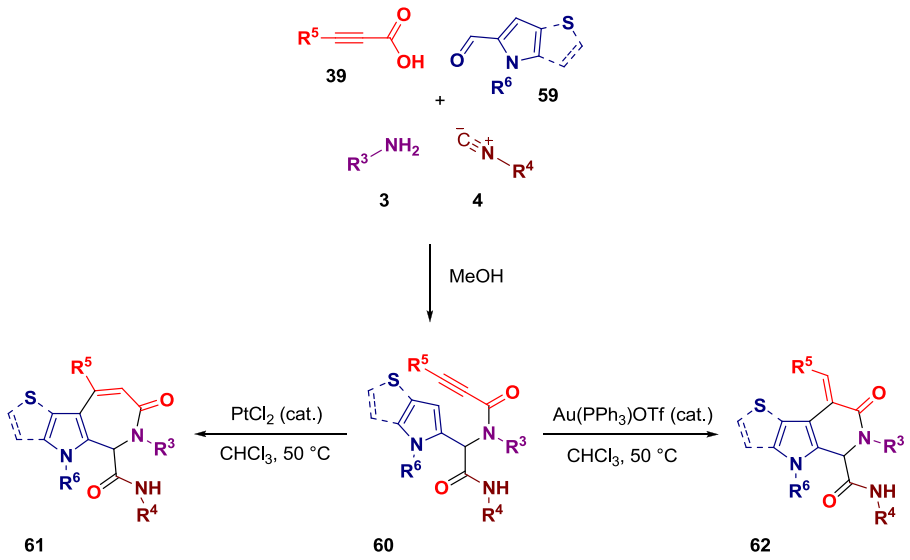
Scheme 15. Synthesis of azepinoindoles **53** and azepinobenzothiophenes **54**.

Another notable extension is obtained when the carbonyl group is put in the 4-position of the indole, resulting in the formation of Ugi adducts **56**. Remarkably, the regioselectivety of their cycloisomerization could be efficiently controlled by the choice of a proper catalytic system. Employing either a cationic Au(I)- or In(III)- catalyst, the ring closure was directed towards an *endo-dig* or an *exo-dig* cyclization respectively, resulting in the formation of azocino[5,4,3-cd]indoles **57** and azepino[5,4,3-cd]indoles **58** (Scheme 16).[28]



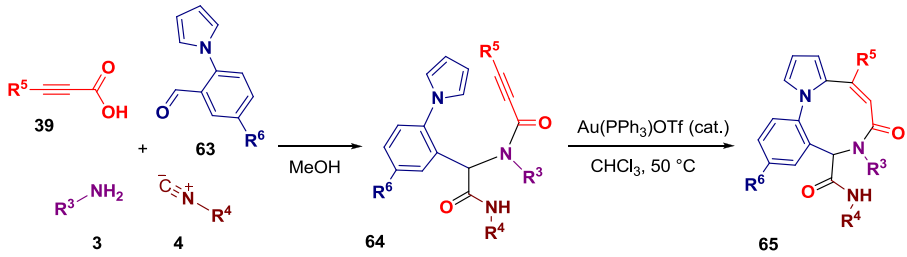
Scheme 16. Synthesis of azocino[5,4,3-cd]indoles **57** and azepino[5,4,3-cd]indoles **58**.

The nucleophilic properties of the indole core are responsible for the ability of the above substrates to undergo transition metal-catalyzed carbocyclizations. The same is true for various pyrrole-based substrates. The pyrrole-2-carbaldehyde-derived Ugi products **60** have been successfully applied for the regioselective synthesis of pyrrolo[2,3-c]azepines **61** and pyrrolo[2,3-c]pyridines **62** via a Pt(II)-/cationic Au(I)-catalysis switch (Scheme 17).[29]



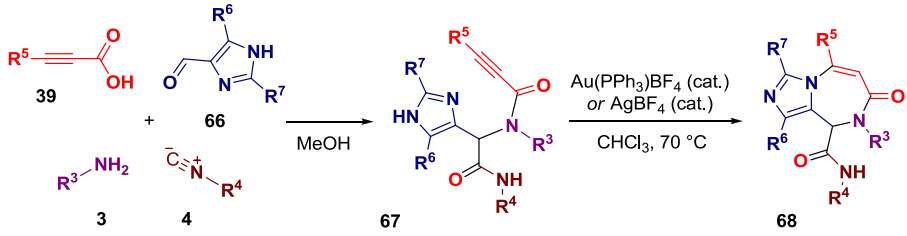
Scheme 17. Synthesis of pyrrolo[2,3-c]azepines **61** and pyrrolo[2,3-c]pyridines **62**.

It is well known that medium-sized rings are difficult to synthesize for enthalpic and entropic reasons. In this regard, our group has demonstrated that even a complex 9-membered ring containing benzo[b]pyrrolo[1,2-i][1,5]diazonine skeleton **65** could be assembled following an Ugi/cationic Au(I)-catalyzed triple-bond hydroarylation sequence, employing the exceptionally high nucleophilicity of the 2-position of the pyrrole ring of Ugi-adduct **64** (Scheme 18).[30]



Scheme 18. Synthesis of benzo[b]pyrrolo[1,2-i][1,5]diazonines **65**.

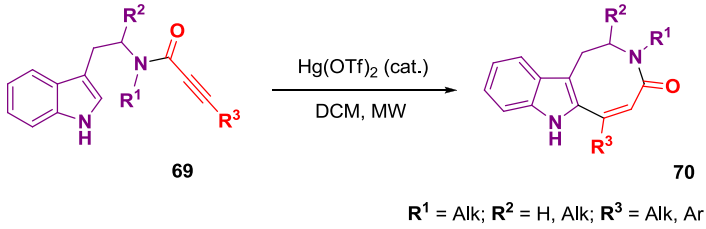
Transition metal-catalyzed post-Ugi cycloisomerization processes are not limited to carbocyclizations. Nitrogen nucleophiles have also been validated through the synthesis of imidazo[1,4]diazepin-7-ones **68** starting from 1*H*-imidazole-4-carbaldehyde-derived Ugi adducts **67** (Scheme 19).[31] Interestingly, both cationic Au(I) and Ag(I) catalysts were found competent to catalyze this post-Ugi heteroannulation.



Scheme 19. Synthesis of imidazo[1,4]diazepin-7-ones **68**.

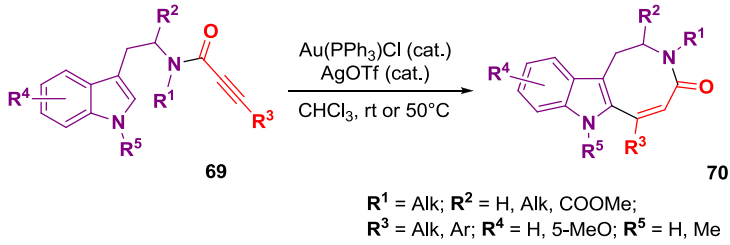
Coming back to indole nucleophiles, our group has a long-standing interest in utilizing its reactivity for cyclizations onto the triple bond. It started in 2009 when a microwave-assisted $Hg(OTf)_2$-catalyzed intramolecular alkyne hydroarylation reaction was disclosed for the synthesis of variously substituted azocino[4,5-b]indoles **70** from propar-

gylamides **69**, which were prepared by amide coupling reaction (Scheme 20).[32]



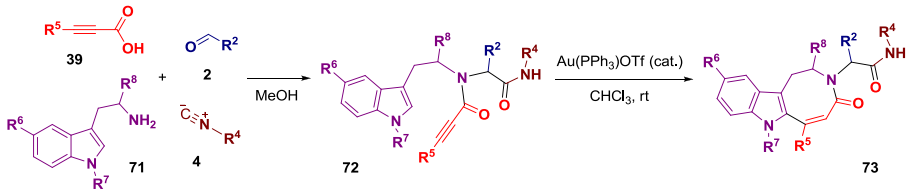
Scheme 20. Synthesis of azocino[4,5-b]indoles **70** via microwave-assisted $Hg(OTf)_2$-catalyzed intramolecular alkyne hydroarylation.

Since most of the inorganic and organic mercury compounds are highly toxic, an alternative catalytic system to replace $Hg(OTf)_2$ in the above process was investigated resulting in the engagement into cationic Au(I) catalysis. With regard to azocino[4,5-b]indole **70** synthesis, the $Au(PPh_3)Cl/AgOTf$ catalytic system was found to be superior to the previously described $Hg(OTf)_2$ catalyst, and hence the substrate scope of the process was significantly expanded (Scheme 21).[33]



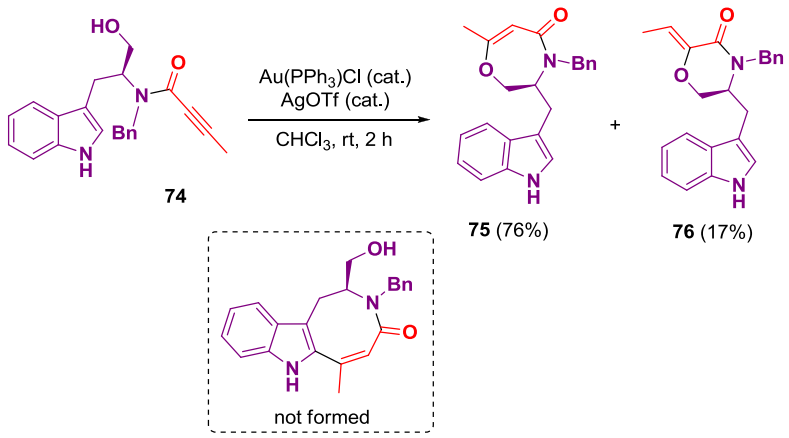
Scheme 21. Synthesis of azocino[4,5-b]indoles **70** via cationic Au(I)-catalyzed intramolecular alkyne hydroarylation.

Simultaneously a diversity-oriented approach was developed towards the synthesis of densely decorated azocino[4,5-b]indoles of type **73**, employing a sequential Ugi reaction/cationic Au(I)-catalyzed intramolecular alkyne hydroarylation (Scheme 22).[34]



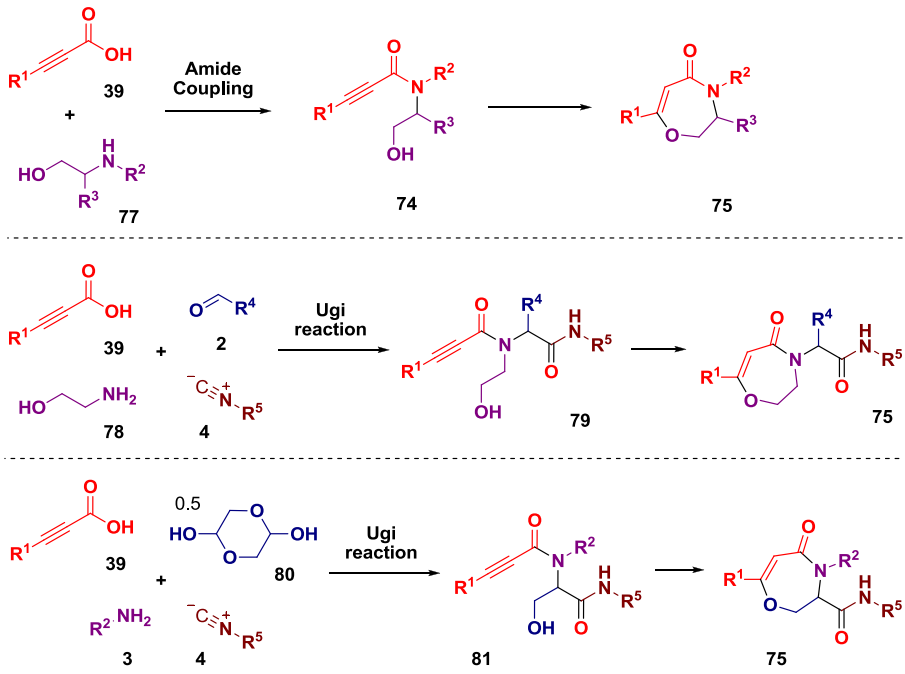
Scheme 22. Synthesis of azocino[4,5-b]indoles **73**.

In the course of the synthesis of azocino[5,4-*b*]indoles **70** through a gold-catalyzed intramolecular triple bond hydroarylation[33] (Scheme 21) another potentially useful transformation was accidentally discovered (Scheme 23). While the common pathway involved the carbocyclization of propargylamides **69** into **70**, the substrate **74**, bearing an alcohol functional group, yielded oxazepine **75** as the major product, along with minor amounts of morpholine **76** (Scheme 23).[35]



Scheme 23. Unexpected formation of oxazepine **75**.

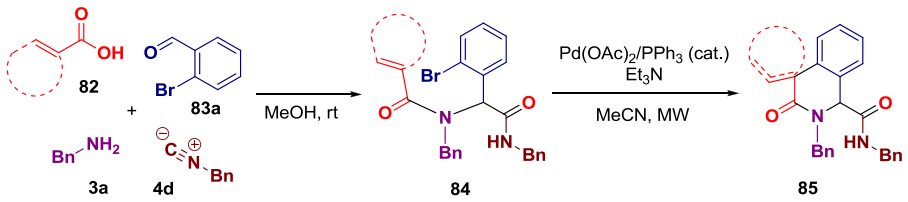
The studies described in **Chapter 3** aim to extend the scope of this approach, in order to establish a general and selective entry to the oxazepine scaffold **75**, starting from three different types of hydroxy-propargylamide substrates **74**, **79** and **81** derived from either amide coupling or four-component Ugi reactions (Scheme 24).[36,37,38]



Scheme 24. Outline of the general strategy for the generation of oxazepines **75**.

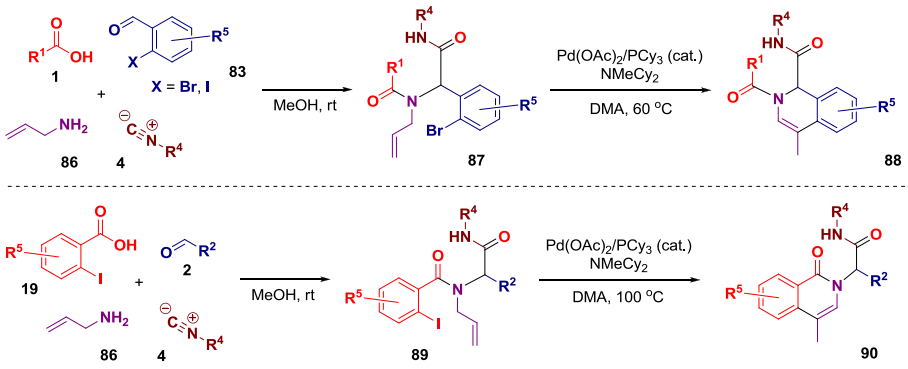
1.3. Heck-type post-Ugi transformations; towards diversity-oriented synthesis of 3-benzazepines

In many cases, the four-component Ugi reaction and the intramolecular Heck coupling proved to be valuable additions to each other. In 2004, Gracias and co-workers combined an α,β-unsaturated carboxylic acid (cyclic and acyclic) **82**, 2-bromobenzaldehyde **83a**, benzyl amine **3a**, and benzyl isocyanide **4d** to generate the Ugi adducts **84** that were further cyclized into isoquinolines **85** upon the action of Pd catalysis (Scheme 25).[39]



Scheme 25. Synthesis of isoquinolines **85**.

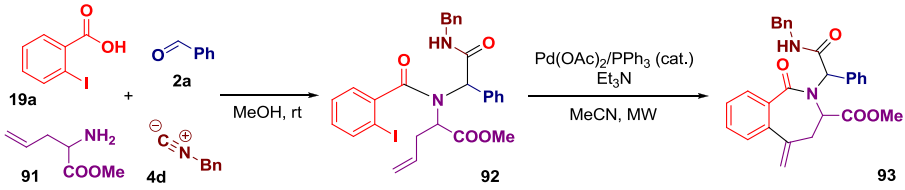
Simultaneously, Yang and co-workers described an efficient two-step Ugi–Heck procedure for the synthesis of two other types of isoquinoline scaffolds **88** and **90** (Scheme 26).[40] In this case, the required Ugi adducts **87** and **89** were prepared by reacting allylamine **86** either with a 2-halobenzaldehyde **83** or with a 2-iodobenzoic acid **19** in the presence of other required Ugi components (Scheme 26).



Scheme 26. Synthesis of isoquinoline derivatives **88** and **90**.

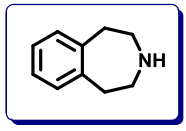
Reacting amine **91**, featuring elongated linker between the amine and olefin functionalities, with 2-iodobenzoic acid **19a**, benzaldehyde **2a** and benzyl isocyanide **4d** affords Ugi adduct **92**. Subsequent intermo-

lecular Heck coupling efficiently assembles the 7-membered ring of 2-benzazepine **93** (Scheme 27).[39]



Scheme 27. Synthesis of 2-benzazepine **93**.

The 2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine commonly referred to as the 3-benzazepine is another related medium ring containing heterocyclic system and a core structural element of many natural and biologically active compounds (Figure 1).[41]



3-Benzazepine

Figure 1.

For example, the 3-benzazepine core is present in many alkaloids (Figure 2) such as aphanorphine, isolated from the blue-green algae, *Aphanizomenon flos-aquae*,[42] lennoxamine, originally isolated from the Chilean barberry, *Berberis darwinii*[43], and cephalotaxine, originally isolated[44] from *Cephalotaxus drupacea* and *Cephalotaxus fortunei.* These compounds inspired many synthetic chemists owing to their unique and challenging structural features.[45,46,47] It should also be

stressed that, although so far no significant biological activity has been reported for all these alkaloids, several naturally occurring esters of cephalotaxine do exhibit promising anticancer[48] and antimalarial[49] properties.

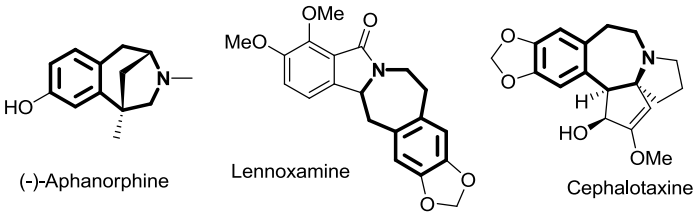


Figure 2. Alkaloids featuring a 3-benzazepine motif.

Various 1-aryl-substituted 3-benzazepines have been explored as dopaminergic agents due to their high affinity to dopamine receptors.[50] The typical compound of this class, fenoldopam, is a first selective peripheral dopamine receptor agonist approved for clinical use to cure severe hypertension.[51] Another important type of biological activity associated with 3-benzazepines is based on their interaction with the serotonine receptors.[52] For example, lorcaserin is an efficient and selective 5-HT_{2C} agonist and has been studied as an anorectic for the treatment of obesity.[53]

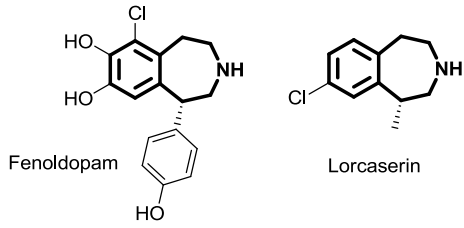
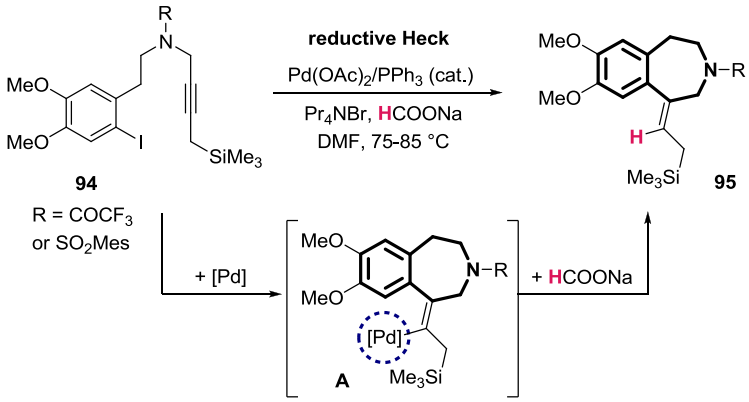


Figure 3. Representative biologically active compounds featuring the 3-benzazepine motif.

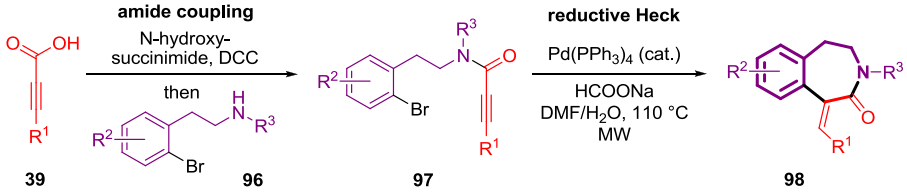
3-Benzazepine has been used as a target motif for a large number of synthetic studies. Successful examples include various types of ring-expansion reactions,[54] insertion of allenes into the Pd−C bond of *ortho*-palladated phenethylamines[55] and heterocyclizations involving either intramolecular reductive amination[56] or transition metal-catalyzed triple-bond hydroamination.[57] Radical,[58] Friedel-Crafts[59] and Heck-type[60] carbocyclizations are also among the most applied methodologies for the 3-benzazepine assembly.

In 1994 Tietze and Schimpf described an efficient route towards 3-benzazepines **95** applying an intramolecular version of the reductive Heck reaction, also referred to as a formal triple bond hydroarylation.[61,62,63,64] In this process, propargylamides of type **94** bearing an aryliodide moiety undergo regioselective 7-*exo-dig* carbocyclization mediated by a Pd catalyst, followed by reduction of the intermediate vinylpalladium species **A** with sodium formate (Scheme 28). In addition to the regioselectivity, the process is also stereoselective producing exclusively 3-benzazepines **95** with the *Z*-configuration of the exocyclic double bond.



Scheme 28. Synthesis of 3-benzazepines **95**.

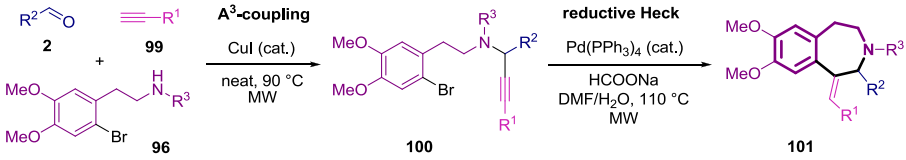
Following the success of Tietze's procedure our group has established a more general protocol that utilizes readily accessible propargylamides **97** derived from 3-substituted propiolic acids **39** and 2-bromophenethylamines **96** for the synthesis of benzazepines **98** (Scheme 29).[65,66,67]



Scheme 29. Synthesis of 3-benzazepines **98**.

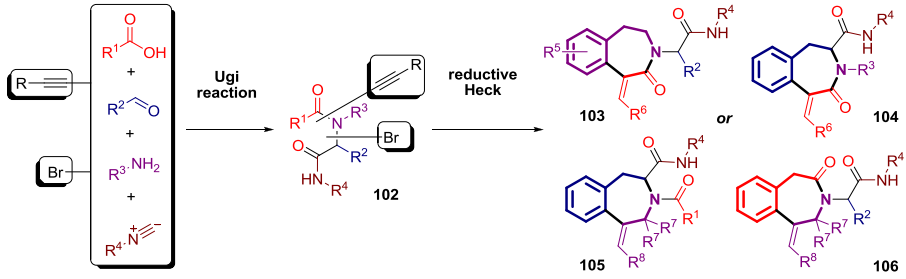
Subsequently we expanded this approach to the use of propargylamine precursors **100** derived from a Cu(I)-catalyzed three-component coupling of an aldehyde **2**, a terminal alkyne **99**, and a 2-bromophenethylamine **96**, commonly referred to as A^3-coupling,[68,69]

aiming to introduce diversity in the resulting 3-benzazepines **101** (Scheme 30).[70]



Scheme 30. Synthesis of 3-benzazepines **101**.

Looking for other unexplored possibilities, we envisaged that the four-component Ugi reaction[71] might provide us with a novel interesting family of propargylamide precursors **102** for the reductive Heck cyclization. 3-Benzazepines **103-106**, featuring different substitution patterns and even more diversity points, could be achieved by varying substituents and shuffling the required functional groups in the components of the Ugi reaction (Scheme 31). **Chapter 4** is devoted to the investigation of the applicability of this Ugi/reductive Heck sequence[72,73] for the diversity-oriented synthesis of 3-benzazepines.

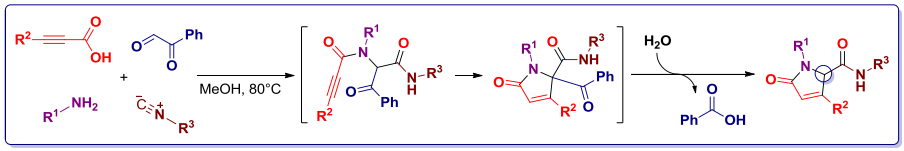


Scheme 31. Strategy towards 3-benzazepines **103-106**.

Chapter 2

This chapter is based on [Assembly of a 1H-Pyrrol-2(5H)-one Core through a Cascade Ugi Reaction/5-*endo-dig* Carbocyclization/Retro-Claisen Fragmentation Process, Anatoly A. Peshkov, Vsevolod A. Peshkov, Zhenghua Li, Olga P. Pereshivko, Erik V. Van der Eycken, *European Journal of Organic Chemistry*, **2014**, 6390–6393].

2. Assembly of a 1*H*-Pyrrol-2(5*H*)-one Core through a Cascade Ugi Reaction/5-*endo-dig* Carbocyclization/Retro-Claisen Fragmentation Process



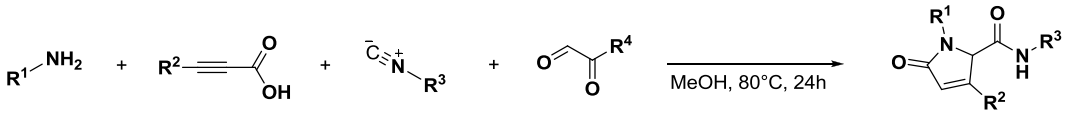
In this chapter we present a novel cascade transformation involving Ugi reaction followed by 5-*endo-dig* carbocyclization and retro-Claisen fragmentation providing an access to 1*H*-pyrrol-2(5*H*)-one core. The operating protocol is very similar to the typical Ugi reaction settings, while the overall outcome results from the application of a 3-substituted propiolic acid and a phenylglyoxal as acid and aldehyde components, respectively. The utility of process is demonstrated through the synthesis of a small library of 5-oxo-2,5-dihydro-1*H*-pyrrole-2-carboxamides.

2.1. Results and discussion

We have started the substrate scope investigation with a screening of various primary amines **3a-f** in a combination with tetrolic acid (**39a**), *tert*-butyl isocyanide (**4a**) and phenylglyoxal (**40a**, monohydrate form). Carrying out these reactions in methanol at 80 °C for 24 h we were able to obtain desired pyrrolones **43a-f** in good to high yields of 62-92 % (Table 1, entries 1-6). Application of different 3-substituted propiolic acids **39b-d** in combination with **3a**, **4a** and **40a** in all cases allowed to maintain the good yields for the target products **43g-i** (Table 1, en-

tries 7-9). In contrast, isocyanide component showed very different performance ranging from good for cyclohexyl isocyanide (**4b**) to moderate for 1,1,3,3-tetramethylbutyl (**4c**) and benzyl (**4d**) isocyanides down to very poor for aromatic 4-methoxyphenyl isocyanide (**4e**) (Table 1, entries 10-13). Next we decided to probe methylglyoxal (**40b**, 40 wt. % in water) in place of phenylglyoxal (**40a**) in order to upgrade the atom economy of the process by sacrificing with a smaller acetyl fragment rather than a bigger benzoyl. However, three representative reactions with **40b** gave substantially diminished yields of the desired products compared to the analogous reactions with **40a** (Table 1, entries 14, 15 and 16 *versus* 1, 2 and 7 respectively).

Table 1. Scope and limitation of a cascade Ugi reaction / 5-*endo*-*dig* carbocyclization / retro-Claisen fragmentation.[a]



3 39 4 40 43

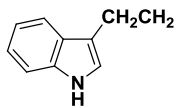
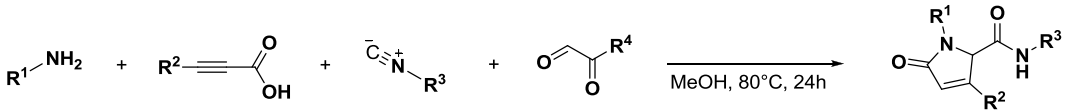
Entry	R^1 (**3**)	R^2 (**39**)	R^3 (**4**)	R^4 (**40**)	**43**	Yield, %[b]
1	Bn (**3a**)	Me (**39a**)	*t*Bu (**4a**)	Ph (**40a**)	**43a**	92
2	PMB (**3b**)	Me (**39a**)	*t*Bu (**4a**)	Ph (**40a**)	**43b**	62
3	Heptyl (**3c**)	Me (**39a**)	*t*Bu (**4a**)	Ph (**40a**)	**43c**	73
4	Cyclopropyl (**3d**)	Me (**39a**)	*t*Bu (**4a**)	Ph (**40a**)	**43d**	72
5	Cyclooctyl (**3e**)	Me (**39a**)	*t*Bu (**4a**)	Ph (**40a**)	**43e**	76
6	 (**3f**)	Me (**39a**)	*t*Bu (**4a**)	Ph (**40a**)	**43f**	64
7	Bn (**3a**)	Et (**39b**)	*t*Bu (**4a**)	Ph (**40a**)	**43g**	89
8	Bn (**3a**)	Pentyl (**39c**)	*t*Bu (**4a**)	Ph (**40a**)	**43h**	80
9	Bn (**3a**)	Ph (**39d**)	*t*Bu (**4a**)	Ph (**40a**)	**43i**	60

Table 1. (continued)

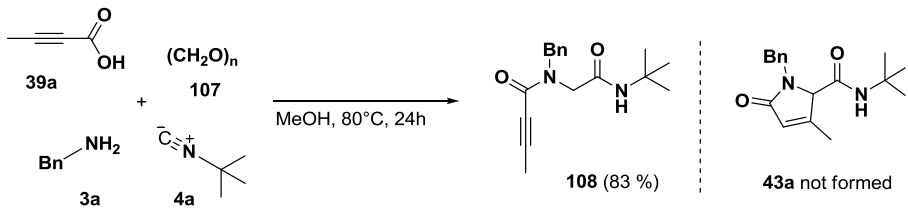


3 39 4 40 43

Entry	R^1 (**3**)	R^2 (**39**)	R^3 (**4**)	R^4 (**40**)	**43**	Yield, %[b]
10[c]	Bn (**3a**)	Me (**39a**)	Cyclohexyl (**4b**)	Ph (**40a**)	**43j**	87
11	Bn (**3a**)	Me (**39a**)	1,1,3,3-Tetramethylbutyl (**4c**)	Ph (**40a**)	**43k**	40
12	Bn (**3a**)	Me (**39a**)	Bn (**4d**)	Ph (**40a**)	**43l**	29
13	Bn (**3a**)	Me (**39a**)	4-$MeOC_6H_4$ (**4e**)	Ph (**40a**)	**43m**	11
14	Bn (**3a**)	Me (**39a**)	*t*Bu (**4a**)	Me (**40b**)	**43a**	68
15	PMB (**3b**)	Me (**39a**)	*t*Bu (**4a**)	Me (**40b**)	**43b**	37
16	Bn (**3a**)	Et (**39b**)	*t*Bu (**4a**)	Me (**40b**)	**43g**	50

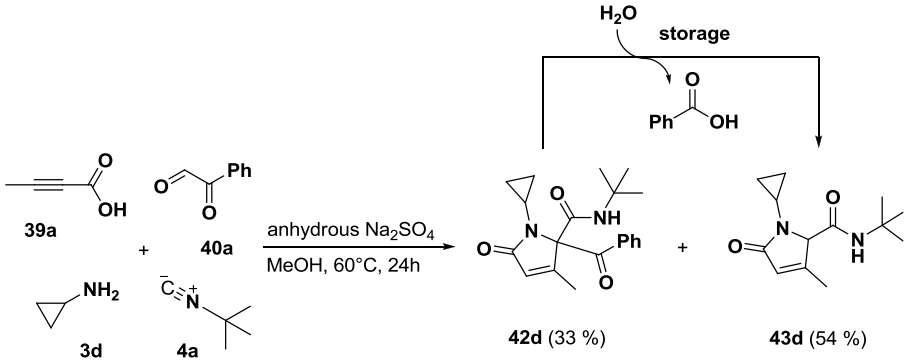
[a] Reactions were carried out on a 0.5 mmol scale in 2 ml of MeOH using equimolar amounts of starting materials. [b] Yield of isolated product. [c] The reaction was conducted at 60 °C.

From the point of view of the overall outcome, both methylglyoxal (**40b**) and phenylglyoxal (**40a**) are used in our process as formaldehyde surrogates. However, the control experiment with paraformaldehyde (**107**) yielded only acyclic Ugi-adduct **108** (Scheme 32), showing that the presence of the glyoxal-derived electron-withdrawing group is essential for the cyclization step and for the overall Ugi reaction / 5-*endo-dig* carbocyclization / retro-Claisen fragmentation process.



Scheme 32. Control experiment with paraformaldehyde **107**.

It is also worth highlighting that in one case we were able to trap and characterize unfragmented pyrrolone **42d**. Conducting the reaction of **39a**, **40a**, **3d**, and **4a** at 60 °C in the presence of anhydrous sodium sulfate led to the isolation of **42d** in 33 % yield in addition to **43d**, which was still obtained as a major product in 54 % yield (Scheme 33). Compound **42d** fully converts into **43d** and benzoic acid during long term storage under ambient conditions.



Scheme 33. Trapping of pyrrolone **42d**.

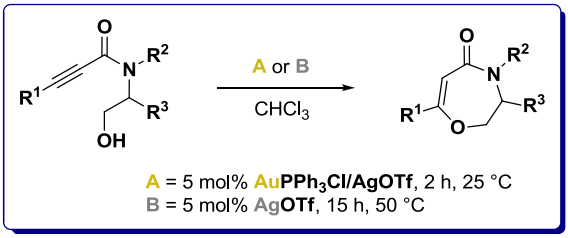
2.2. Conclusions

In conclusion, we have successfully combined elements of rational design and serendipity to elaborate a novel cascade transformation involving Ugi reaction followed by enolization-triggered 5-*endo*-*dig* carbocyclization and retro-Claisen fragmentation leading to 1*H*-pyrrol-2(5*H*)-ones. The described methodology is operationally simple and utilizes readily available primary amines, 3-substituted propiolic acids, isocyanides and phenylglyoxal as starting materials.

Chapter 3

This chapter is based on [Gold- and Silver-Catalyzed 7-*endo*-*dig* Cyclizations for the Synthesis of Oxazepines, Anatoly A. Peshkov, Anton A. Nechaev, Olga P. Pereshivko, Jan L. Goeman, Johan Van der Eycken, Vsevolod A. Peshkov, Erik V. Van der Eycken, *European Journal of Organic Chemistry*, **2015**, 4190–4197].

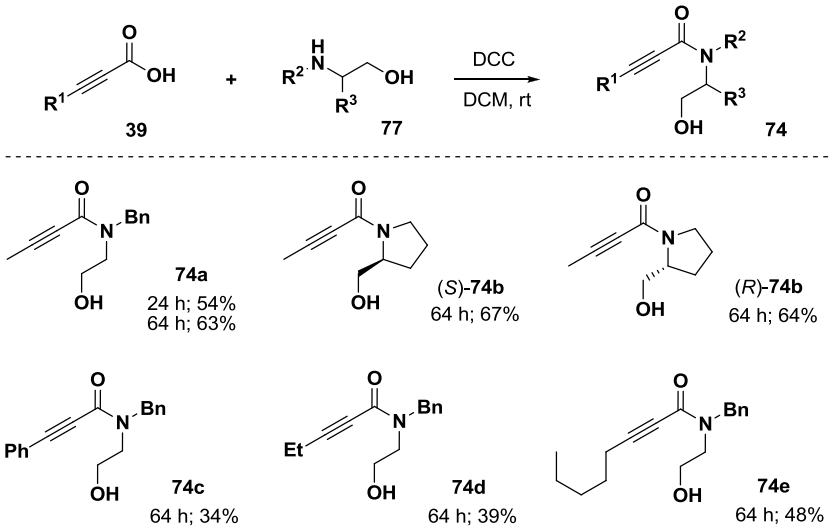
3. Gold and Silver Catalyzed 7-*endo-dig* Cyclizations for the Synthesis of Oxazepines



In this chapter we describe a comprehensive study on gold- and silver-catalyzed cycloisomerizations of hydroxypropargylamides into oxazepines. Three different types of hydroxypropargylamide substrates derived from either amide coupling or Ugi reaction have been validated providing selective and general access to a medium-ring oxazepine core.

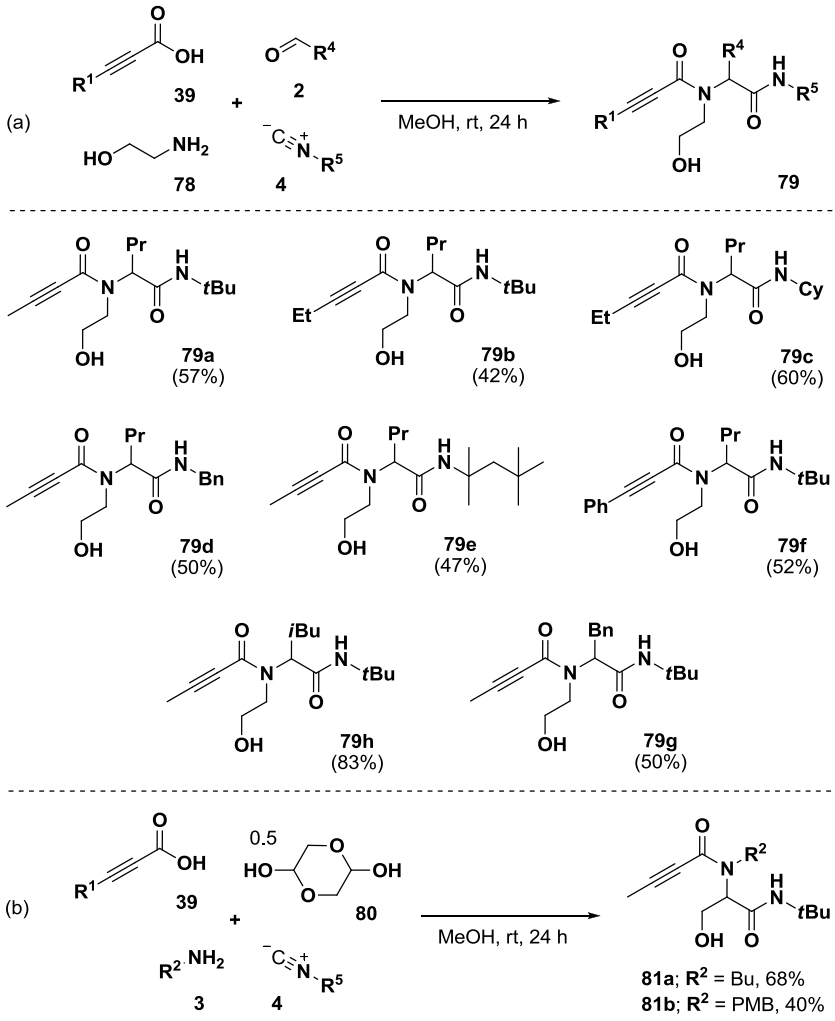
3.1. Results and discussion

We have started with the synthesis of several hydroxypropargylamides **74** through the direct amide coupling of unprotected secondary aminoalcohols **77** with 3-substituted propiolic acids **39**. All reactions proceeded with moderate to good efficiency utilizing DCC as a convenient coupling reagent (Scheme 34).



Scheme 34. Synthesis of hydroxypropargylamides **74** through the amide coupling reaction.

Another set of hydroxypropargylamide substrates **79** and **81** was attained by a four-component Ugi reaction that at the same time acted as a potent diversification tool. Incorporating the hydroxyl function into the amine component yielded hydroxypropargylamides of type **79** (Scheme 35a). The application of glycolaldehyde dimer **80** provided hydroxypropargylamides of type **81** (Scheme 35b).

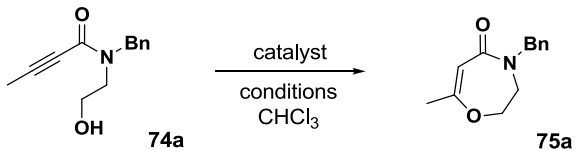


Scheme 35. Synthesis of hydroxypropargylamides **79** and **81** through Ugi reaction.

Next we performed a catalyst screening using hydroxypropargylamide **74a** as a model substrate (Table 2). The application of gold(I)triphenylphosphine chloride in combination with silver(I) triflate, forming *in situ* catalytically active cationic gold, led to a full conversion

of **74a** within 2 h at 25 °C allowing to obtain the desired oxazepine **75a** in 96 % isolated yield (Table 2, entry 1). Silver triflate alone was also competent to catalyze this transformation (Table 2, entries 2-4), although, an extended time and an elevated reaction temperature of 50 °C were required to achieve full conversion of **74a**, finally providing **75a** in 91 % isolated yield (Table 2, entry 4). At the same time gold(I)triphenylphosphine chloride alone, copper(II) triflate and p-toluenesulfonic acid failed to catalyze this process (Table 2, entries 5, 6 and 7). Applying gold(III) chloride, the desired oxazepine product **75a** could be obtained in moderate yield but it is difficult to drive reaction to completion (Table 2, entries 8-10). Probably, the reaction slows down due to the degradation of the catalyst that occurs during prolonged reaction time.

Table 2. Catalyst screening for the cycloisomerization of hydroxypropargylamide **74a** into oxazepine **75a**.[a]

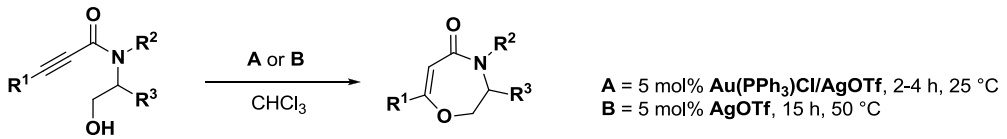


Entry	Catalyst	Conditions	Conversion [%][b]	Yield [%][c]
1 (conditions A)	**5 mol% $Au(PPh_3)Cl/AgOTf$**	**2 h, 25 °C**	**100**	**96**
2	5 mol% AgOTf	24 h, 25 °C	82	78
3	5 mol% AgOTf	2 h, 50 °C	93	85
4 (conditions B)	**5 mol% AgOTf**	**15 h, 50 °C**	**100**	**91**
5	5 mol% $Au(PPh_3)Cl$	24 h, 25 °C or 3 h, 50 °C	0	0
6	5 mol% $Cu(OTf)_2$	24 h, 25 °C or 3 h, 50 °C	0	0
7	20 mol% $TsOH \cdot H_2O$	15 h, 50 °C	0	0
8	5 mol% $AuCl_3$	2 h, 25 °C	39	35
9	5 mol% $AuCl_3$	2 h, 50 °C	47	40
10	5 mol% $AuCl_3$	24 h, 50 °C	60	51

[a] The reactions were run on 0.3 mmol scale in 1.2 mL of dry $CHCl_3$. [b] Determined from ^1H NMR of a crude reaction mixture. [c] Yield of isolated product.

With these results in hand, we explored the substrate scope. The cycloisomerizations of all prepared hydroxypropargylamides **74**, **79** and **81** were attempted under both cationic gold (condition A) and silver triflate (condition B) catalysis in all cases delivering the target oxazepines **75** in good to high yields with comparable efficiency (Table 3). Importantly, no racemization occurred in the reactions with substrates (*S*)-**74b** and (*R*)-**74b** derived from enantiopure prolinols, demonstrating the mild character of both gold- and silver-catalyzed protocols (Table 3, entries 1 and 2). For the silver-catalyzed cyclizations of hydroxypropargylamides **74c** and **79f** bearing a phenyl group on the triple bond, and hydroxypropargylamide **81a** an increased catalyst loading was required in order to reach full conversion (Table 3, entries 3, 11 and 14). Finally, it is important to stress that all reaction exclusively led to the formation of oxazepine **75** *via* 7-*endo-dig* cycloisomerization.

Table 3. Cycloisomerizations of hydroxypropargylamide precursors **74**, **79** and **81** into oxazepines **75**.[a]



74, **79** or **81** — **75**

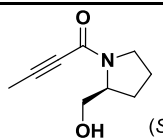
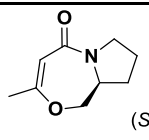
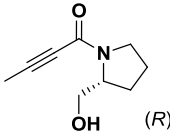
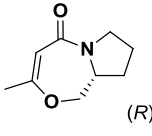
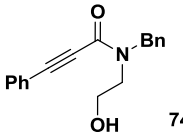
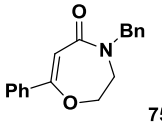
Entry	Hydroxypropargylamide **74**, **79** or **81**	Oxazepine **75**	Yield [%][b]	
			Conditions A	Conditions B
1	 (*S*)-**74b**	 (*S*)-**75b**	95	89
2	 (*R*)-**74b**	 (*R*)-**75b**	96	-[c]
3	 **74c**	 **75c**	73	74[d]

Table 3. (continued)

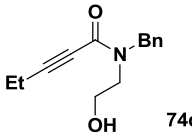
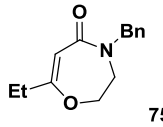
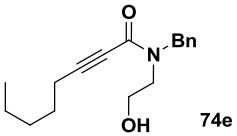
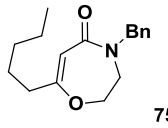
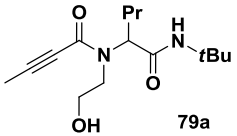
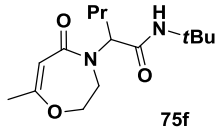
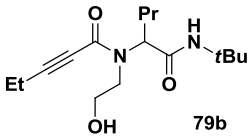
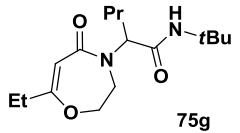
Entry	Hydroxypropargylamide **74**, **79** or **81**	Oxazepine **75**	Yield [%][b]	
			Conditions A	Conditions B
4	 **74d**	 **75d**	84	86
5	 **74e**	 **75e**	90	86
6	 **79a**	 **75f**	89	89
7	 **79b**	 **75g**	75	64

Table 3. (continued)

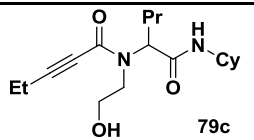
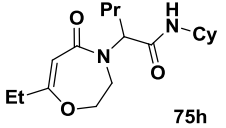
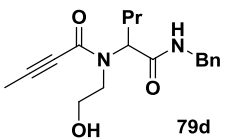
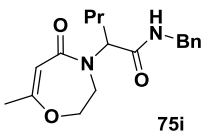
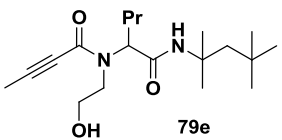
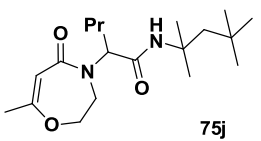
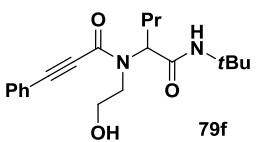
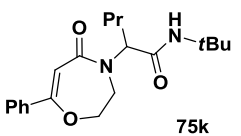
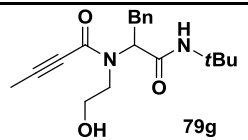
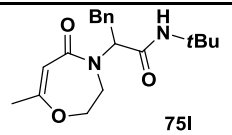
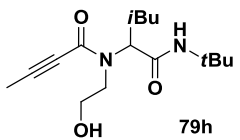
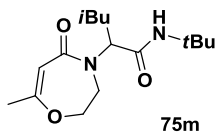
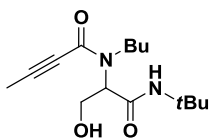
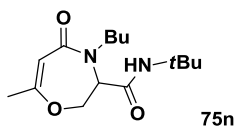
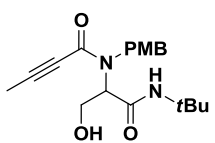
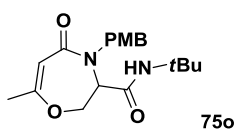
Entry	Hydroxypropargylamide **74**, **79** or **81**	Oxazepine **75**	Yield [%][b]	
			Conditions A	Conditions B
8	 **79c**	 **75h**	77	74
9	 **79d**	 **75i**	88	82
10	 **79e**	 **75j**	87	84
11	 **79f**	 **75k**	89	78[d]

Table 3. (continued)

Entry	Hydroxypropargylamide **74**, **79** or **81**	Oxazepine **75**	Yield [%][b]	
			Conditions A	Conditions B
12	 **79g**	 **75l**	84	86
13	 **79h**	 **75m**	95	85
14	 **81a**	 **75n**	82[e]	89[d]
15	 **81b**	 **75o**	82	79

[a] The reactions were run on 0.3 mmol scale in 1.2 mL of dry $CHCl_3$. [b] Yield of isolated product. [c] The reaction was not performed. [d] 20 mol% of AgOTf was used and the reaction was run for 20 h. [e] The reaction was run for 16 h.

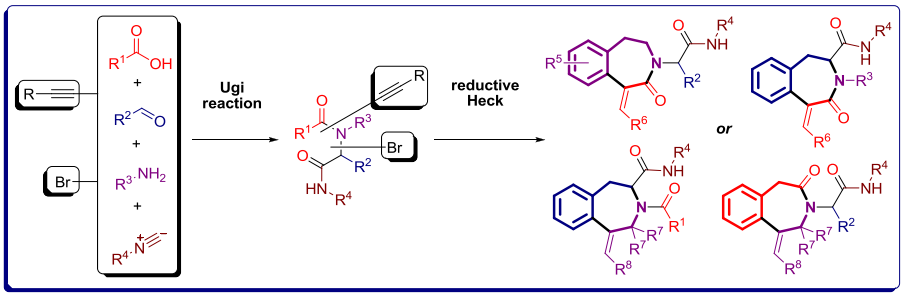
3.2. Conclusions

In summary, we have successfully established an efficient and selective route towards the synthesis of oxazepines through the cycloizomerization of readily accessible hydroxypropargylamides that occurs in the presence of either gold or silver catalyst. The scope of the process has been thoroughly explored using various types of substrates, resulting in the generation of a small yet diverse library of target compounds.

Chapter 4

This chapter is based on [Diversification of the 3-benzazepine scaffold applying Ugi/reductive Heck sequence, Anatoly A. Peshkov, Vsevolod A. Peshkov, Olga P. Pereshivko, Erik V. Van der Eycken, *Tetrahedron,* **2015***, 71,* 3863–3871].

4. Diversification of the 3-Benzazepine Scaffold Applying Ugi / Reductive Heck Sequence



In this chapter, we evaluate a two-step sequence involving Ugi reaction followed by reductive Heck cyclization in order to provide access to a 3-benzazepine framework in a diversity-oriented fashion. Several aspects related to the substrate scope and the optimal distribution of the required functional groups have been addressed, resulting in the construction of a small library of the title compounds, featuring four distinct types of substitution pattern.

4.1. Results and discussion

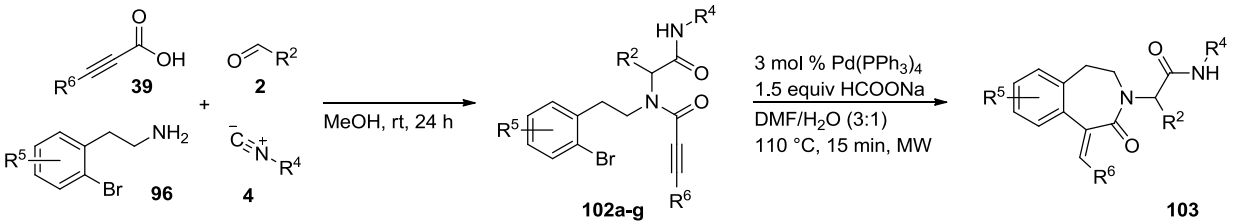
We have started our synthetic exercises with a straightforward combination of 3-substituted propiolic acids **39** and 2-bromophenethylamines **96** complemented with various aldehydes **2** and isocyanides **4**. In all cases the required propargylamide precursors **102a-g** and the final 3-benzazepines of type **103** could be successfully prepared with good to high yields (Table 4). The substrate scope proved to be quite flexible allowing the successful application of both aliphatic and aromatic aldehydes **2** and isocyanides **4**. In addi-

tion both alkyl and aryl substituents at the 3-position of the propiolic acid **39** were found to be tolerable.

Switching to the use of a ketone **109** as carbonyl component gave diminished 35% yield of Ugi product **102h** despite the elevated reaction temperature of 70 °C and extended reaction time of 72 h. Nonetheless subsequent reductive Heck cyclization delivered 3-benzazepine **103h** in a fairly good yield of 56% (Scheme 36).

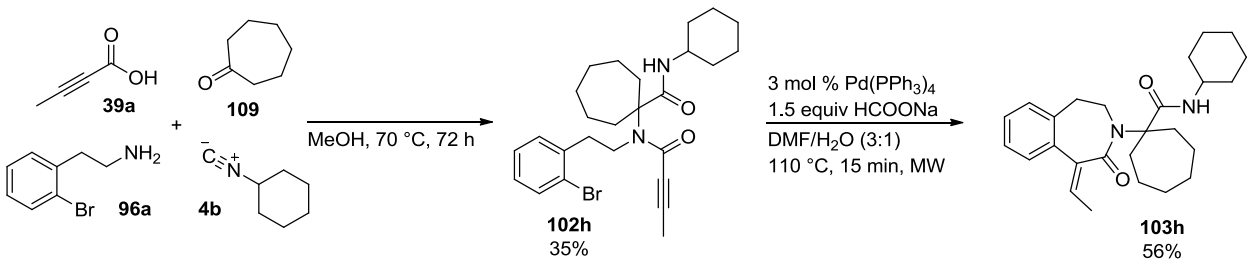
Next we compared the reactivity of 2-bromo- and 2-iodophenethylamines **96b** and **96b'** as well as of corresponding propargylamides **102i** and **102i'** derived from them. The 2-bromophenethylamine **96b** beat the iodo- analog **96b'** in the Ugi step, while the 2-iodophenethylamine-derived propargylamide **102i'** proved to be somewhat better then **102i** in the reductive Heck ring-closure (Table 5).

Table 4. Ugi/reductive Heck sequence for the synthesis of 3-benzazepines of type **103**.[a]



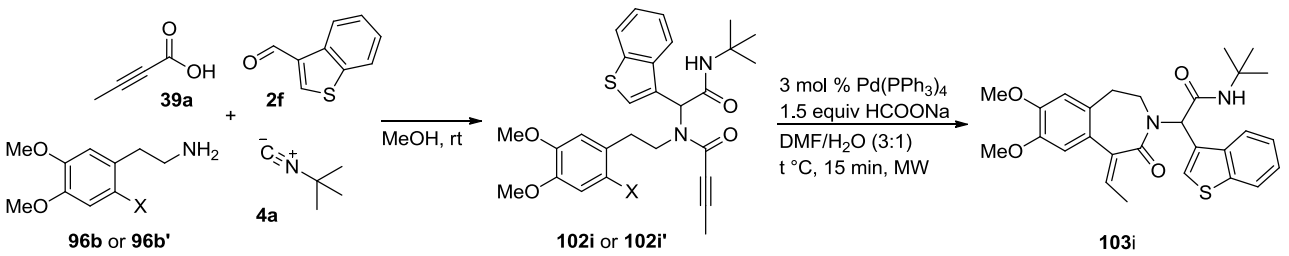
Entry	Propiolic acid **39**; R^6	2-bromophenethyl-amine **96**; R^5	Aldehyde **2**; R^2	Isocyanide **4**; R^4	Ugi product **102** (yield, %)[b]	Reductive Heck pro-duct **103** (yield, %)[b]
1	Me	H	Pr	Bn	**102a** (88)	**103a** (90)
2	Me	H	4-CNC_6H_4	1,1,3,3-tetramethylbutyl	**102b** (91)	**103b** (79)
3	Me	4,5-$(MeO)_2$	Ph	*t*Bu	**102c** (93)	**103c** (76)
4	Et	H	*i*Bu	Cy	**102d** (93)	**103d** (77)
5	Hexyl	H	*i*Bu	2-naphthyl	**102e** (86)	**103e** (81)
6	Ph	4,5-$(MeO)_2$	Pr	*t*Bu	**102f** (80)	**103f** (87)
7	4-$MeOC_6H_4$	H	Bn	*t*Bu	**102g** (43)	**103g** (63)

[a] The Ugi reactions were run on 0.5 mmol scale in 2 mL of MeOH; the reductive Heck reactions were run on 0.15-0.45 mmol scale. [b] Yield of isolated product.



Scheme 36. Use of a ketone as carbonyl component in the Ugi/reductive Heck sequence.

Table 5. Comparison of 2-bromo- and 2-iodophenethylamines **96b** and **96b'** in the Ugi/reductive Heck sequence.[a]



Entry	X	Ugi reaction time, h	Ugi product (yield, %)[b]	Reductive Heck t, °C	Reductive Heck product (yield, %)[b]
1	Br	24	**102i** (71)	110	**103i** (79)
2	I	48	**102i'** (46)	90	**103i** (91)

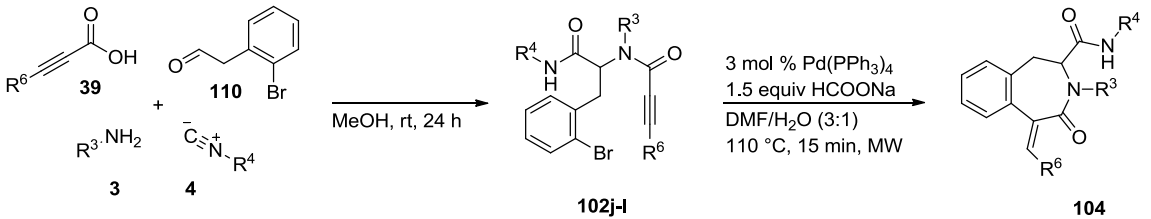
[a] The Ugi reactions were run on 0.5 mmol scale in 2 mL of MeOH; the reductive Heck reactions were run on 0.2 mmol scale.
[b] Yield of isolated product.

Moving the bromoaryl functionality from the amine to the aldehyde component while maintaining the propiolic acids as source of the triple bond provided another interesting type of Ugi adducts **102j-l**. The subsequent reductive Heck cyclization resulted in the efficient synthesis of densely decorated 3-benzazepines of type **104** in up to 95% yield (Table 6).

When a primary propargylamine **111a** was used as triple bond source in combination with 2-bromophenylacetaldehyde **110**, benzoic acid **1a** and *tert*-butyl isocyanide **4a** a moderate yield of 56% for the Ugi adduct **102m** was obtained. The subsequent conversion into the target 3-benzazepine **105** gave 49% yield (Scheme 37).

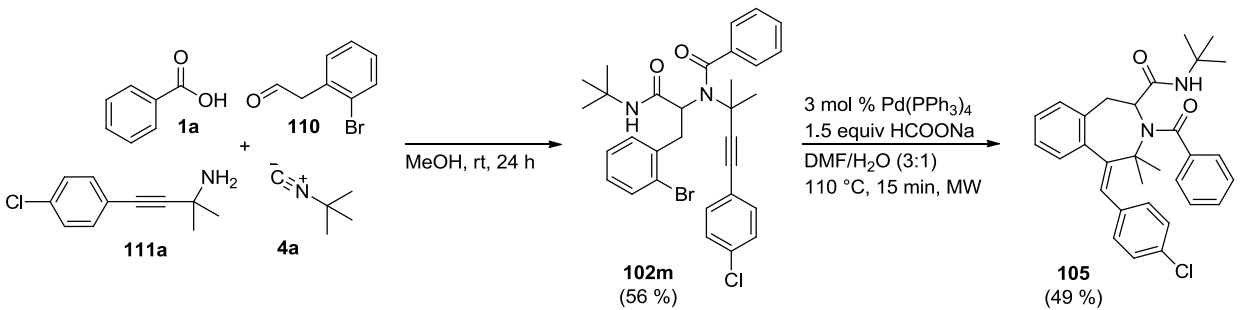
Finally, the triple bond was delivered by the primary propargylamine **111** and the arylbromide moiety by the carboxylic acid **112**. This combination proved to be the most unfavorable as already the Ugi step proceeded with just a moderate efficiency. More disappointedly, the crucial reductive Heck step gave the desired benzazepines **106** in low yields of 24% and 31%, despite the full conversion of the starting propargylamides **102n,o** (Table 7).

Table 6. Ugi/reductive Heck sequence for the synthesis of 3-benzazepines of type **104**.[a]



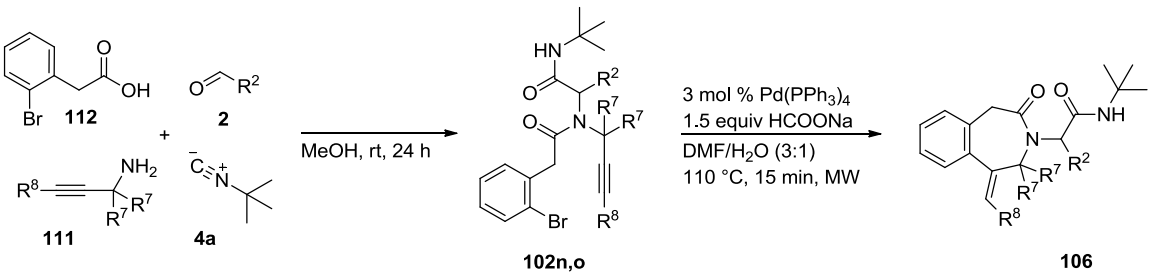
Entry	Propiolic acid **39**; R^6	Amine **3**; R^3	Isocyanide **4**; R^4	Ugi product **102** (yield, %)[b]	Reductive Heck product **104** (yield, %)[b]
1	Me	Bn	Cy	**102j** (63)	**104a** (95)
2	Et	Cyclopropyl	4-$MeOC_6H_4$	**102k** (70)	**104b** (77)
3	Ph	Pentyl	*t*Bu	**102l** (66)	**104c** (88)

[a] The Ugi reactions were run on 0.5 mmol scale in 2 mL of MeOH; the reductive Heck reactions were run on 0.2-0.3 mmol scale. [b] Yield of isolated product.



Scheme 37. Ugi/reductive Heck sequence for the synthesis of 3-benzazepine **105**.

Table 7. Ugi/reductive Heck sequence for the synthesis of 3-benzazepines of type **106**.

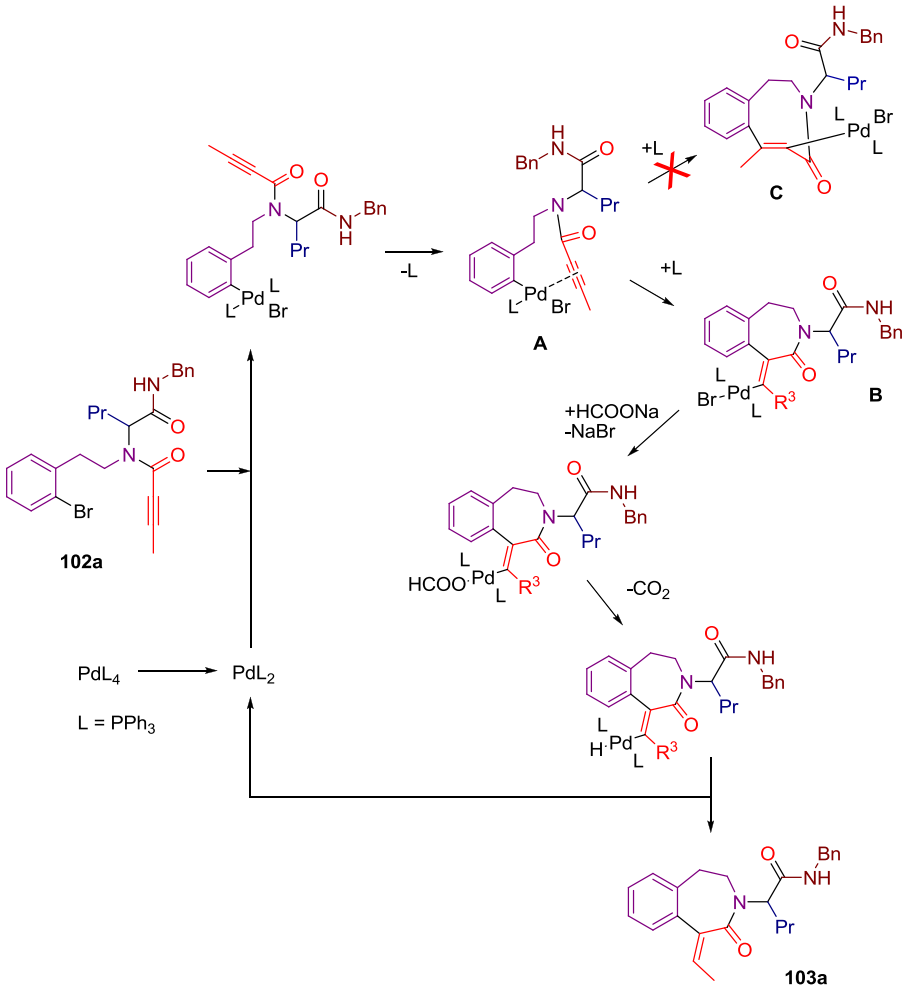


Entry	Propargylamine **111**; R^7, R^8	Aldehyde **2**; R^2	Ugi product **102** (yield, %)	Reductive Heck product **106** (yield, %)
1	H, Ph	Pr	**7n** (52)[a]	**11a** (24)[b]
2	Me, 4-ClC_6H_4	4-FC_6H_4	**7o** (33)[c]	**11b** (31)[c]

[a] Yield of crude product.

[b] Yield of isolated product calculated based on crude starting material.

[c] Yield of isolated product.



Scheme 38. Proposed mechanistic pathway of the reductive Heck reaction

A possible pathway for the intramolecular reductive Heck reaction exemplified by the synthesis of 3-benzazepine **103a** is presented on Scheme 38. The starting Ugi adduct **102a** undergoes oxidative addition to the palladium (0) catalyst followed by the formation of the arylpalladium π-complex **A**. In the next step, **A** is transformed into a vi-

nyl palladium complex **B** via simultaneous *syn*-insertion of the triple bond. This is followed by the ligand exchange, extrusion of CO_2 and the reductive elimination providing final **103a**. As can be evident from the mechanism, this strategy exclusively provides *exo*-cyclized seven-membered products possessing the *Z*-configuration of the exocyclic double bond. The *endo*-cyclization via a hypothetical intermediate **C** is fairly unlikely due to the high strain exerted by the *trans* geometry around the double bond in the medium-sized ring. Importantly, the structure of the representative 3-benzazepine synthesized by this methodology has been previously unambiguously assigned using COSY, HMBC, HMQC and NOE NMR techniques.[41d,55a]

4.2. Conclusions

In summary, we have demonstrated that the Ugi reaction could be successfully applied for the synthesis of various propargylamides that are suitable substrates for the reductive Heck cyclization leading to the 3-benzazepine scaffold. Four different types of 3-benzazepines were assembled showing that the overall efficiency of the process significantly depends on the initial distribution of the required functional groups in the Ugi reaction components.

General conclusions and perspectives

The work described in this thesis belongs to one of the major research program pursued by our group that is devoted to the diversity-oriented synthesis of biologically important heterocycles. The core concept of this work is to highlight and broaden the synthetic potential of 3-substituted propiolic acids in a four-component Ugi reaction. This interest was driven by multiple possibilities of upgrading the resulting Ugi-adducts into heterocycles that arise from the presence of the propiolic acid-originated triple bond and, if necessary, other functionalities.

In the first project (***Chapter 2***) we have efficiently extended the array of enolization-driven post-transformations of Ugi adducts by a novel one-pot cascade Ugi reaction / 5-*endo*-*dig* carbocyclization / retro-Claisen fragmentation process leading to 1*H*-pyrrol-2(5*H*)-ones. The operating protocol for this process is very similar to the typical Ugi reaction settings, while the overall outcome results from the application of a 3-substituted propiolic acid and a phenylglyoxal as acid and aldehyde components, respectively.

Following our long-standing interests in medium ring systems as well as in the activation of the triple bond by a coinage metal salts we invoked Ag(I)- and cationic Au(I) catalysis to establish a general route towards oxazepine core through the cycloizomerizations of hydroxypropargylamides derived from either Ugi reaction or amide coupling (***Chapter 3***).

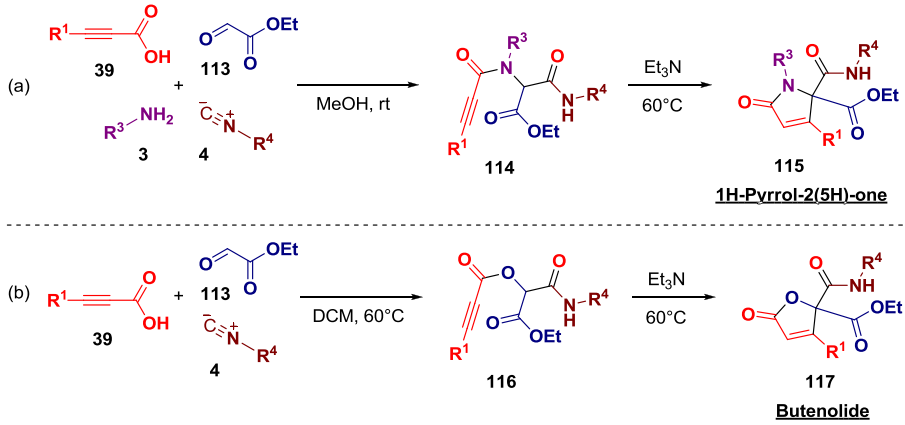
Finally, in the last project (***Chapter 4***) we extended the applicability of our reductive Heck procedure leading to 3-benzazepine scaffold to the use of Ugi reaction-derived propargylamides that helped to achieve an exceptionally high level of diversity in the resulting library of target products.

Thus, it can be assumed that with regard to propiolic acid-derived Ugi adducts, the main goal of this thesis was successfully achieved, as they indeed proved to allow a large variety of post-transformations, which spands from classical enolization-driven cycloisomerizations (***Chapter 2***) to more modern Pd(0)-, Ag(I)- and cationic Au(I)-catalyzed transformations (***Chapers 3 and 4***).

With regard to the scope, it is rather clear that the four-component Ugi reaction already offers tremendous potential for diversification. Furthermore, we have shown that shuffling the required functional groups in the components of the Ugi reaction leads to altering the substitution pattern in the desired heterocyclic scaffolds (Chapers 3 and 4), opening the way to the concept of ‘‘libraries of libraries’’ of products resembling natural products and pharmaceuticals. Therefore, these current findings not only complement the existing array of synthetic approaches but also offer some concepts that are important for designing and implementing further strategies.

The next task would be to transfer some of these methodologies to a three-component Passerini reaction.[74] This proved to be somewhat challenging as our initial attempt to substitute the Ugi reaction with a Passerini reaction in the enolization-triggered cyclization, described in ***Chapter 2***, met with failure, as a complex mixture of reaction products was obtained. However, when we switched from phenylglyoxal (**40a**) to ethyl glyoxylate (**113**) the formation of both Ugi **114** and Passerini

116 adducts could be successfully observed. To our delight these adducts could be *in situ* converted into 1*H*-pyrrol-2(5*H*)-ones **115** and butenolides **117**, respectively (Scheme 39). The study of the scope and limitations of these new processes are currently underway.



Scheme 39. Multicomponent Ugi and Passerini reactions in the tandem processes leading to 1*H*-pyrrol-2(5*H*)-ones **115** and butenolides **117**.

Experimental part

General information

^{1}H and ^{13}C NMR spectra were recorded with 300 and 75 MHz respectively using Bruker Avance instrument. The ^{1}H and ^{13}C chemical shifts are reported in parts per million relative to tetramethylsilane using the residual solvent signal as the internal reference.

The microwave irradiation experiments were carried out in a dedicated CEM-Discover monomode microwave apparatus, operating at a frequency of 2.45 GHz with continuous irradiation power from 0 to 300 W and utilization of the standard absorbance level of 300 W. The reactions were carried out in 10 mL glass tubes, sealed with a Teflon septum and placed in the microwave cavity. The reactions were irradiated at the required set temperature for the stipulated time and then cooled to ambient temperature with air jet cooling.

Low resolution mass spectra were recorded using a Hewlett-Packard 5989A mass spectrometer (EI and CI mode).

High-resolution EI mass spectra were recorded on a Kratos MS50TC system with a resolution of 10000. The ion source temperature was 150-250 °C, as required.

High-resolution ESI mass spectra for **Chapter 3** were recorded using an Agilent 1100 series HPLC coupled to an Agilent 6220A TOF-MSD, equipped with ESI/APCI ionization source.

High-resolution ESI mass spectra for **Chapter 4** were acquired on a quadrupole orthogonal acceleration time-of-flight mass spectrometer (Synapt G2 HDMS, Waters, Milford, MA). Samples were infused at 3 μL/min and spectra were obtained in positive ionization mode with a resolution of 15000 (FWHM) using leucine enkephalin as lock mass.

Reversed phase HPLC separation was performed on a Waters Delta 600 analytical/preparative system equipped with a Waters 996 Photo Diode Array detector using Alltech C18 Prevail (5 μm×150 nm×22 mm) preparative column.

Infrared (IR) spectra were recorded neat on a Bruker ALPHA FT-IR Spectrometer, and wavelengths are reported in cm^{-1}.

Specific rotations were measured using PolAAr 20 automatic polarimeter.

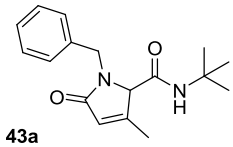
Melting points were recorded on a Reichert Thermovar apparatus and are uncorrected.

All required reagents, starting materials and solvents were purchased from commercial sources and used without further purification.

Chapter 2

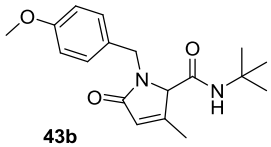
General procedure for the Ugi reaction followed by 5-*endo*-*dig* carbocyclization and retro-Claisen fragmentation

3-Substituted propiolic acid **39** (0.5 mmol) was dissolved in methanol (2 mL) followed by addition of phenylglyoxal monohydrate (**40a**) (76 mg, 0.5 mmol), amine **3** (0.5 mmol) and isocyanide **4** (0.5 mmol). The resulting mixture was stirred at 80 °C for 24 h in a sealed screw cap vial. The resulting mixture was concentrated and subjected to the column chromatography to give desired product **43**.



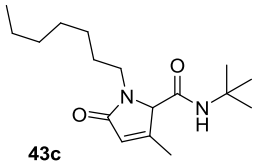
43a

1-benzyl-*N*-*tert*-butyl-3-methyl-5-oxo-2,5-dihydro-1*H*-pyrrole-2-carboxamide (43a). The title compound (132 mg, 92 %) was isolated by column chromatography on silicagel using heptane-EtOAc (40 %) as eluent. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.41-7.13 (m, 5H), 5.91 (pentet, J = 1.5 Hz, 1H), 5.47 (bs, 1H), 4.82 (d, J = 14.8 Hz, 1H), 4.27 (d, J = 14.8 Hz, 1H), 4.22-4.17 (m, 1H), 2.05-2.00 (m, 3H), 1.20 (s, 9H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 173.2, 165.5, 157.2, 136.9, 129.1, 128.6, 128.1, 122.3, 71.3, 51.6, 46.1, 28.5, 14.6; HRMS (EI, $[M]^+$) for $C_{17}H_{22}N_2O_2^{\bullet+}$ calcd. 286.1676, found 286.1674.



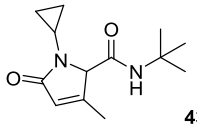
43b

***N-tert*-butyl-1-(4-methoxybenzyl)-3-methyl-5-oxo-2,5-dihydro-1*H*-pyrrole-2-carboxamide (43b).** The title compound (98 mg, 62 %) was isolated by column chromatography on basic alumina using heptane-EtOAc (50-70 %) as eluent. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.22-7.14 (m, 2H), 6.87-6.80 (m, 2H), 5.87 (pentet, J = 1.5 Hz, 1H), 5.45 (bs, 1H), 4.78 (d, J = 14.7 Hz, 1H), 4.21-4.11 (m, 2H), 3.78 (s, 3H), 2.02-1.98 (m, 3H), 1.21 (s, 9H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 173.1, 165.6, 159.5, 157.1, 130.0, 129.0, 122.3, 114.4, 71.1, 55.4, 51.6, 45.4, 28.5, 14.6; HRMS (EI, $[M]^+$) for $C_{18}H_{24}N_2O_3^{\bullet+}$ calcd. 316.1781, found 316.1817.



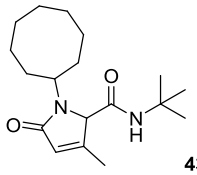
43c

***N-tert*-butyl-1-heptyl-3-methyl-5-oxo-2,5-dihydro-1*H*-pyrrole-2-carboxamide (43c).** The title compound (107 mg, 73 %) was isolated by column chromatography on basic alumina using heptane-EtOAc (50-70 %) as eluent. ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.82 (pentet, J = 1.5 Hz, 1H), 5.58 (bs, 1H), 4.35-4.28 (m, 1H), 3.67 (dt, J = 8.0, 13.9 Hz, 1H), 3.05-2.90 (m, 1H), 2.07-1.98 (m, 3H), 1.59-1.44 (m, 2H), 1.33-1.14 (m, 17H), 0.90-0.77 (m, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 172.9, 166.0, 156.2, 122.7, 71.3, 51.7, 41.8, 31.8, 29.0, 28.7, 28.4, 26.9, 22.6, 14.4, 14.1; HRMS (EI, $[M]^+$) for $C_{17}H_{30}N_2O_2^{\bullet+}$ calcd. 294.2302, found 294.2307.



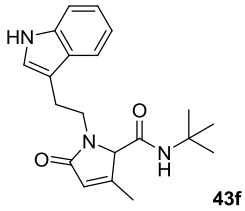
43d

***N-tert*-butyl-1-cyclopropyl-3-methyl-5-oxo-2,5-dihydro-1*H*-pyrrole-2-carboxamide (43d).** The title compound (85 mg, 72 %) was isolated by column chromatography on basic alumina using heptane-EtOAc (50 %) as eluent. ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.81 (pentet, J = 1.5 Hz, 1H), 5.51 (bs, 1H), 4.24-4.19 (m, 1H), 2.75-2.62 (m, 1H), 2.04-1.99 (m, 3H), 1.32 (s, 9H), 0.90-0.64 (m, 4H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 174.0, 166.2, 156.5, 122.9, 72.2, 51.8, 28.7, 25.0, 14.5, 5.3, 5.2; HRMS (EI, $[M]^+$) for $C_{13}H_{20}N_2O_2^{\bullet+}$ calcd. 236.1519, found 236.1515.



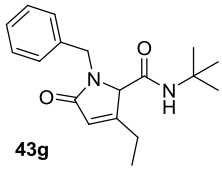
43e

***N-tert*-butyl-1-cyclooctyl-3-methyl-5-oxo-2,5-dihydro-1*H*-pyrrole-2-carboxamide (43e).** The title compound (116 mg, 76 %) was isolated by column chromatography on basic alumina using heptane-EtOAc (20-40 %) as eluent. ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.80 (pentet, J = 1.5 Hz, 1H), 5.61 (bs, 1H), 4.37-4.31 (m, 1H), 4.07-3.91 (m, 1H), 2.03-1.97 (m, 3H), 1.97-1.42 (m, 14H), 1.30 (s, 9H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 173.6, 167.1, 156.9, 123.3, 70.8, 54.6, 51.6, 32.2, 31.9, 28.6, 26.7, 26.3, 26.0, 25.6, 24.4, 14.3; HRMS (EI, $[M]^+$) for $C_{18}H_{30}N_2O_2^{\bullet+}$ calcd. 306.2302, found 306.2302.



43f

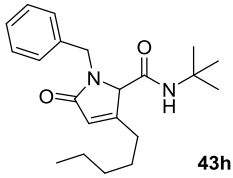
1-(2-(1*H*-indol-3-yl)ethyl)-*N*-tert-butyl-3-methyl-5-oxo-2,5-dihydro-1*H*-pyrrole-2-carboxamide (43f). The title compound (108 mg, 64 %) was isolated by column chromatography on basic alumina using EtOAc as eluent. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.25 (bs, 1H), 7.65-7.56 (m, 1H), 7.39-7.31 (m, 1H), 7.23-7.15 (m, 1H), 7.15-7.06 (m, 2H), 5.87 (pentet, J = 1.5 Hz, 1H), 5.50 (bs, 1H), 4.30-4.24 (m, 1H), 4.12-3.98 (m, 1H), 3.54-3.38 (m, 1H), 3.15-2.93 (m, 2H), 2.04-1.97 (m, 3H), 1.21 (s, 9H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 173.3, 166.0, 156.7, 136.4, 127.4, 122.7, 122.3, 121.9, 119.7, 118.8, 112.6, 111.4, 71.8, 51.7, 42.2, 28.5, 24.3, 14.4; HRMS (EI, $[M]^+$) for $C_{20}H_{25}N_3O_2^{\bullet+}$ calcd. 339.1941, found 339.1969.



43g

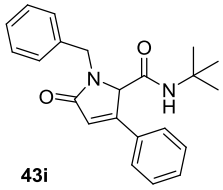
1-benzyl-*N*-*tert*-butyl-3-ethyl-5-oxo-2,5-dihydro-1*H*-pyrrole-2-carboxamide (43g). The title compound (134 mg, 89 %) was isolated by column chromatography on silicagel using heptane-EtOAc (40-50 %) as eluent. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.39-7.20 (m, 5H), 5.90 (q, J = 1.7 Hz, 1H), 5.51 (bs, 1H), 4.81 (d, J = 14.9 Hz, 1H), 4.33-4.22 (m, 2H), 2.40-2.27 (m, 2H), 1.19 (s, 9H), 1.16 (t, J = 7.4 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 173.2, 165.6, 163.2, 136.9, 129.1, 128.6,

128.0, 120.3, 70.6, 51.6, 46.0, 28.4, 21.9, 11.8; HRMS (EI, $[M]^+$) for $C_{18}H_{24}N_2O_2^{\bullet+}$ calcd. 300.1832, found 300.1844.



43h

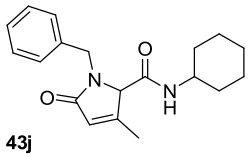
1-benzyl-*N*-*tert*-butyl-5-oxo-3-pentyl-2,5-dihydro-1*H*-pyrrole-2-carboxamide (43h). The title compound (137 mg, 80 %) was isolated by column chromatography on basic alumina using heptane-EtOAc (20-40 %) as eluent. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.39-7.18 (m, 5H), 5.89 (q, J = 1.6 Hz, 1H), 5.51 (bs, 1H), 4.80 (d, J = 14.9 Hz, 1H), 4.29 (d, J = 14.9 Hz, 1H), 4.24 (d, J = 1.4 Hz, 1H), 2.38-2.23 (m, 2H), 1.68-1.43 (m, 2H), 1.38-1.21 (m, 4H), 1.19 (s, 9H), 0.95-0.78 (m, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 173.2, 165.6, 161.9, 137.0, 129.1, 128.5, 128.0, 120.9, 70.6, 51.5, 46.0, 31.4, 28.4, 27.2, 22.4, 14.0; HRMS (EI, $[M]^+$) for $C_{21}H_{30}N_2O_2^{\bullet+}$ calcd. 342.2302, found 342.2301.



43i

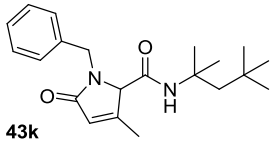
1-benzyl-*N*-*tert*-butyl-5-oxo-3-phenyl-2,5-dihydro-1*H*-pyrrole-2-carboxamide (43i). The title compound (105 mg, 60 %) was isolated by column chromatography on basic alumina using heptane-EtOAc (20-40 %) as eluent. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.61-7.51 (m, 2H), 7.42-7.24 (m, 8H), 6.48 (d, J = 1.2 Hz, 1H), 5.37 (bs, 1H), 5.08 (d, J = 14.9 Hz, 1H), 4.81 (d, J = 1.2 Hz, 1H), 4.18 (d, J = 14.9 Hz, 1H), 1.11 (s, 9H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 171.4, 165.5, 155.9, 136.7,

130.7, 130.6, 129.00, 128.95, 128.7, 128.0, 127.1, 120.7, 68.8, 51.7, 45.3, 28.3; HRMS (EI, $[M]^+$) for $C_{22}H_{24}N_2O_2^{\bullet+}$ calcd. 348.1832, found 348.1842.



43j

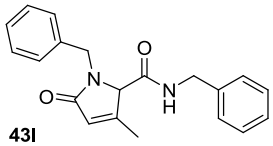
1-benzyl-*N*-cyclohexyl-3-methyl-5-oxo-2,5-dihydro-1*H*-pyrrole-2-carboxamide (43j). The reaction was conducted at 60 °C. The title compound (136 mg, 87 %) was isolated by column chromatography on silicagel using heptane-EtOAc (40-60 %) as eluent. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.41-7.12 (m, 5H), 6.05 (d, J = 8.2 Hz, 1H), 5.90 (pentet, J = 1.5 Hz, 1H), 5.02 (d, J = 14.9 Hz, 1H), 4.30-4.24 (m, 1H), 4.07 (d, J = 14.9 Hz, 1H), 3.79-3.59 (m, 1H), 2.06-1.99 (m, 3H), 1.86-1.53 (m, 5H), 1.41-0.93 (m, 5H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 173.0, 165.4, 157.0, 136.6, 129.0, 128.4, 128.0, 122.3, 70.0, 48.7, 45.5, 32.8, 25.4, 25.01, 24.95, 14.5; HRMS (EI, $[M]^+$) for $C_{19}H_{24}N_2O_2^{\bullet+}$ calcd. 312.1832, found 312.1829.



43k

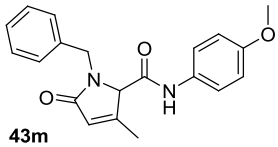
1-benzyl-3-methyl-5-oxo-*N*-(2,4,4-trimethylpentan-2-yl)-2,5-dihydro-1*H*-pyrrole-2-carboxamide (43k). The title compound (68 mg, 40 %) was isolated by column chromatography on basic alumina using heptane-EtOAc (30 %) as eluent. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.39-7.18 (m, 5H), 5.89 (pentet, J = 1.5 Hz, 1H), 5.58 (bs, 1H), 4.90 (d, J = 14.9 Hz, 1H), 4.24-4.14 (m, 2H), 2.06-1.99 (m, 3H), 1.62 (d, J

= 15.0 Hz, 1H), 1.43 (d, J = 15.0 Hz, 1H), 1.34 (s, 3H), 1.23 (s, 3H), 0.93 (s, 9H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 173.2, 165.1, 157.2, 136.9, 129.2, 128.6, 128.1, 122.2, 71.2, 55.8, 52.5, 46.0, 31.7, 31.6, 28.8, 28.3, 14.8; HRMS (EI, $[M]^+$) for $C_{21}H_{30}N_2O_2^{\bullet+}$ calcd. 342.2302, found 342.2293.



43l

***N*,1-dibenzyl-3-methyl-5-oxo-2,5-dihydro-1*H*-pyrrole-2-carboxamide (43l).** The title compound (47 mg, 29 %) was isolated by column chromatography on basic alumina using heptane-EtOAc (10-50 %) as eluent. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.36-7.23 (m, 6H), 7.23-7.12 (m, 4H), 6.74 (t, J = 5.8 Hz, 1H), 5.79 (pentet, J = 1.5 Hz, 1H), 5.00 (d, J = 14.9 Hz, 1H), 4.42 (dd, J = 6.1 Hz, 1H), 4.36-4.24 (m, 2H), 4.01 (d, J = 14.9 Hz, 1H), 2.03-1.99 (m, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 172.9, 166.4, 156.7, 137.9, 136.4, 129.1, 128.9, 128.5, 128.1, 127.9, 127.8, 122.5, 69.8, 45.5, 43.6, 14.6; HRMS (EI, $[M]^+$) for $C_{20}H_{20}N_2O_2^{\bullet+}$ calcd. 320.1519, found 320.1563.



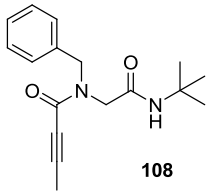
43m

1-benzyl-*N*-(4-methoxyphenyl)-3-methyl-5-oxo-2,5-dihydro-1*H*-pyrrole-2-carboxamide (43m). The pure title compound (18 mg, 11 %) was obtained after column chromatography on basic alumina with ether-EtOAc (75 %) as eluent followed by column chromatography on silicagel with heptane-EtOAc (75 %) as eluent. ^{1}H NMR (300 MHz,

$CDCl_3$): δ 8.06 (bs, 1H), 7.43-7.19 (m, 7H), 6.88-6.78 (m, 2H), 5.94 (pentet, J = 1.5 Hz, 1H), 5.04 (d, J = 14.9 Hz, 1H), 4.45-4.39 (m, 1H), 4.25 (d, J = 14.9 Hz, 1H), 3.79 (s, 3H), 2.11-2.07 (m, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 173.2, 164.4, 157.0, 156.9, 136.4, 130.3, 129.2, 128.6, 128.2, 122.6, 121.9, 114.2, 70.8, 55.6, 45.9, 14.7; HRMS (EI, $[M]^+$) for $C_{20}H_{20}N_2O_3^{\bullet+}$ calcd. 336.1468, found 336.1503.

Control experiment with paraformaldehyde

Tetrolic acid (**39a**) (84 mg, 1 mmol) and paraformaldehyde (**107**) (30 mg) were dissolved in methanol (4 mL) followed by addition of benzylamine (**3a**) (107 mg, 1 mmol) and *tert*-butyl isocyanide (**4a**) (83 mg, 1 mmol). The resulting mixture was stirred at 80 °C for 24 h in a sealed screw cap vial. The resulting mixture was concentrated and subjected to the column chromatography to give Ugi adduct **108** (238 mg, 83 %).



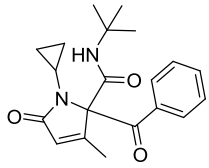
108

***N*-benzyl-*N*-(2-(*tert*-butylamino)-2-oxoethyl)but-2-ynamide (108).** Mixture of rotamers ~ 2:1.[75] ^{1}H NMR (300 MHz, $CDCl_3$): 7.42-7.22 (m, 5H), 5.97 (bs, 0.67H), 5.38 (bs, 0.33H), 4.88 (s, 1.33H), 4.63 (s, 0.67H), 4.05 (s, 0.67H), 3.80 (s, 1.33H), 2.04 (s, 2H), 1.99 (s, 1H), 1.27 (s, 6H), 1.20 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 167.1, 166.9, 155.5, 155.4, 136.3, 135.7, 129.1, 128.9, 128.8, 128.2, 128.1, 127.9, 91.0, 90.9, 72.9, 72.7, 53.9, 53.3, 51.4, 51.3, 49.8, 49.4, 28.6, 28.4,

4.1, 4.0; MS(CI): m/z (relative intensity) 287 ([M+H]$^+$, 82), 214 (100), 172 (16).

Trapping of the pyrrolone 42d

Tetrolic acid (**39a**) (42 mg, 0.5 mmol) was dissolved in anhydrous methanol (2 mL) followed by addition of phenylglyoxal monohydrate (**40a**) (76 mg, 0.5 mmol), cyclopropylamine (**3d**) (29 mg, 0.5 mmol) and *tert*-butyl isocyanide (**4a**) (42 mg, 0.5 mmol). Then anhydrous Na_2SO_4 (0.5 g) was added and the mixture was stirred at 60 °C for 24 h in a sealed screw cap vial. The Na_2SO_4 was filtered off and washed with EtOAc. The combined filtrate was gently concentrated under reduced pressure keeping the water bath of the rotovap at ambient temperature. Column chromatography on silicagel with heptane-EtOAc (40-60 %) as eluent consecutively provided **42d** (56 mg, 33 %) and **43d** (64 mg, 54 %).



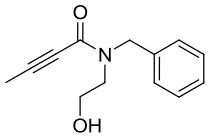
42d

2-benzoyl-*N*-*tert*-butyl-1-cyclopropyl-3-methyl-5-oxo-2,5-dihydro-1*H*-pyrrole-2-carboxamide (42d). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.44 (bs, 1H), 7.69-7.60 (m, 2H), 7.58-7.49 (m, 1H), 7.42-7.32 (m, 2H), 6.18 (q, J = 1.5 Hz, 1H), 2.40-2.28 (m, 1H), 1.95 (d, J = 1.5 Hz, 3H), 1.42 (s, 9H), 0.61-0.40 (m, 4H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 200.1, 175.2, 162.6, 155.5, 137.6, 133.7, 128.8, 128.4, 126.6, 84.3, 52.2, 28.6, 25.6, 13.5, 4.8, 4.7; HRMS (EI, [M]$^+$) for $C_{20}H_{24}N_2O_3^{\bullet+}$ calcd. 340.1781, found 340.1827.

Chapter 3

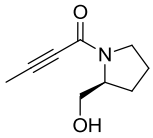
General Procedure for the Synthesis of hydroxypropargylamides 74 through the amide coupling reaction

3-Substituted propiolic acid (2.2 mmol) was dissolved in dry DCM (10 mL) followed by addition of appropriate aminoethanol (2 mmol) and DCC (2.3 mmol). The resulting mixture was stirred at rt for 64 h in a sealed screw cap vial. The subsequently formed precipitate of N,N'-dicyclohexylurea was filtered off and washed with DCM. The combined organic layers were concentrated and subjected to column chromatography on silica gel.



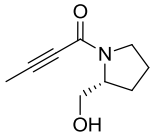
74a

***N*-benzyl-*N*-(2-hydroxyethyl)but-2-ynamide** (**74a**): Elution with heptane/EtOAc (50→100%) delivered pure **74a** as a ~ 3:7 mixture of rotamers.[75] Yield: 274 mg, 63%. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.45-7.15 (m, 5H), 4.87 (s, 1.4H), 4.71 (s, 0.6H), 3.82-3.57 (m, 2.6H), 3.54-3.07 (m, 2.4H), 2.08-1.93 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 156.3, 155.5, 136.8, 136.3, 128.9, 128.7, 128.04, 127.96, 127.5, 90.3, 89.9, 73.3, 73.2, 60.9, 60.5, 54.0, 50.2, 48.2, 47.4, 4.1; HRMS (EI): m/z $[M]^+$ for $C_{13}H_{15}NO_2^{\bullet+}$ calcd. 217.1097; found 217.1118.



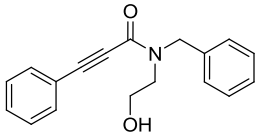
(*S*)-**74b**

(*S*)-1-(2-(hydroxymethyl)pyrrolidin-1-yl)but-2-yn-1-one ((*S*)-**74b**): Elution with pure EtOAc delivered pure (*S*)-**74b** as a ~ 1:4 mixture of rotamers.[75] Yield: 224 mg, 67%. ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.70 (bd, J = 6.1 Hz, 0.8H), 4.27-4.05 (m, 1H), 3.94-3.81 (m, 0.8H), 3.80-3.50 (m, 3H), 3.50-3.37 (m, 0.2H), 2.98 (bs, 0.2H), 2.20-1.75 (m, 6.2H), 1.74-1.58 (m, 0.8H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 155.1, 153.2, 89.7, 87.4, 74.4, 74.1, 66.4, 64.0, 61.1, 60.4, 49.7, 46.8, 28.7, 27.7, 23.9, 22.6, 4.00, 3.97; HRMS (EI): m/z $[M]^+$ for $C_9H_{13}NO_2^{\bullet+}$ calcd. 167.0941; found 167.0952.



(*R*)-**74b**

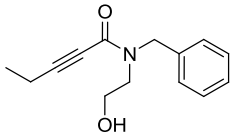
(*R*)-1-(2-(hydroxymethyl)pyrrolidin-1-yl)but-2-yn-1-one ((R)-**74b**): Elution with pure EtOAc delivered pure (*R*)-**74b** as a ~ 1:4 mixture of rotamers.[75] Yield: 214 mg, 64%.



74c

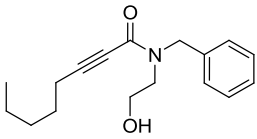
***N*-benzyl-*N*-(2-hydroxyethyl)-3-phenylpropiolamide** (**74c**): Elution with DCM/Et_2O (20%) delivered pure **74c** as a ~ 3:7 mixture of rotamers.[75] Yield: 190 mg, 34%. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.59-7.27 (m, 10H), 4.96 (s, 1.4H), 4.78 (s, 0.6H), 3.87-3.80 (m, 0.6H), 3.79-3.70 (m, 2H), 3.60-3.53 (m, 1.4H); ^{13}C NMR (75 MHz, $CDCl_3$): δ

156.2, 155.3, 136.7, 136.2, 132.5, 132.4, 130.3, 130.1, 128.9, 128.7, 128.55, 128.52, 128.14, 128.06, 127.64, 127.58, 120.4, 120.2, 91.3, 90.9, 81.6, 81.5, 61.2, 60.8, 54.3, 50.5, 48.6, 47.8; HRMS (EI): m/z $[M]^+$ for $C_{18}H_{17}NO_2^{\bullet+}$ calcd. 279.1254; found 279.1223.



74d

***N*-benzyl-*N*-(2-hydroxyethyl)pent-2-ynamide** (**74d**): Elution with heptane/EtOAc (80%) delivered pure **74d** as a ~ 3:7 mixture of rotamers.[75] Yield: 180 mg, 39%. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.45-7.15 (m, 5H), 4.87 (s, 1.4H), 4.72 (s, 0.6H), 3.82-3.74 (m, 0.6H), 3.73-3.59 (m, 2H), 3.54-3.42 (m, 1.4H), 3.05 (bs, 1H), 2.44-2.29 (m, 2H), 1.25-1.12 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 156.4, 155.5, 136.8, 136.3, 128.8, 128.7, 128.1, 128.0, 127.6, 95.6, 95.1, 73.4, 73.3, 61.0, 60.6, 54.1, 50.3, 48.4, 47.5, 12.83, 12.75, 12.69; HRMS (EI): m/z $[M]^+$ for $C_{14}H_{17}NO_2^{\bullet+}$ calcd. 231.1254; found 231.1262.



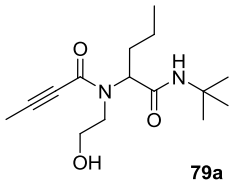
74e

***N*-benzyl-*N*-(2-hydroxyethyl)oct-2-ynamide** (**74e**): Elution with heptane/EtOAc (50→80%) delivered pure **74e** as a ~ 3:7 mixture of rotamers.[75] Yield: 262 mg, 48%. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.41-7.18 (m, 5H), 4.88 (s, 1.4H), 4.72 (s, 0.6H), 3.82-3.74 (m, 0.6H), 3.73-3.58 (m, 2H), 3.53-3.42 (m, 1.4H), 2.39-2.27 (m, 2H), 1.65-1.44 (m, 2H), 1.41-1.19 (m, 4H), 0.95-0.76 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 156.4, 155.5, 136.8, 136.3, 128.8, 128.7, 128.1, 127.9, 127.52, 127.47, 94.6, 94.1, 74.0, 73.9, 60.9, 60.7, 54.1, 50.3, 48.4, 47.5,

31.04, 30.95, 27.5, 27.3, 22.1, 22.0, 18.91, 18.89, 13.9, 13.8; HRMS (EI): m/z $[M]^+$ for $C_{17}H_{23}NO_2^{\bullet+}$ calcd. 273.1723; found 273.1738.

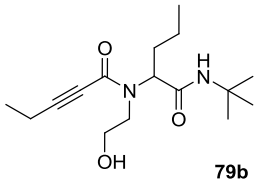
General Procedure for the Synthesis of hydroxypropargylamides 79 through the Ugi reaction

3-Substituted propiolic acid (1.5 mmol) was placed in a screw cap vial and dissolved in methanol (2 mL) followed by addition of aldehyde (1.5 mmol), ethanolamine (92 mg, 1.5 mmol) and isocyanide (1.5 mmol). The mixture was stirred at room temperature for 24 h. Upon completion of reaction time the resulting mixture was diluted with DCM and evaporated with silica followed by column chromatography delivering pure **79**.



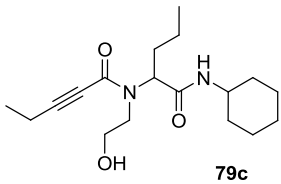
79a

***N-tert*-butyl-2-(*N*-(2-hydroxyethyl)but-2-ynamido)pentanamide** (**79a**): Elution with heptane/EtOAc/MeOH (50:50:1) delivered pure **79a** as a ~ 3:7 mixture of rotamers.[75] Yield: 241 mg, 57%. ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.51-6.21 (m, 1H), 4.62-4.46 (m, 0.3H), 4.38 (t, J = 7.8 Hz, 0.7H), 4.05-3.48 (m, 4H), 2.03 (s, 0.9H), 2.02 (s, 2.1H), 1.99-1.70 (m, 2H), 1.43-1.21 (m, 11H), 1.02-0.90 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.5, 169.7, 156.7, 156.0, 91.4, 90.7, 73.4, 73.3, 63.3, 62.5, 61.2, 59.1, 51.7, 51.6, 50.1, 31.3, 30.2, 28.5, 28.4, 19.5, 13.84, 13.78, 4.15, 4.12; HRMS (ESI): m/z $[M+H]^+$ for $C_{15}H_{27}N_2O_3^+$ calcd. 283.2016; found 283.2020.



79b

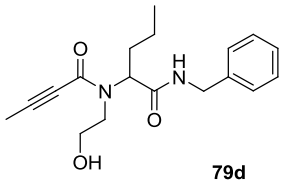
***N*-(1-(*tert*-butylamino)-1-oxopentan-2-yl)-*N*-(2-hydroxyethyl)pent-2-ynamide** (**79b**): Elution with heptane/EtOAc/MeOH (50:50:1) delivered pure **79b** as a ~ 1:3 mixture of rotamers.[75] Yield: 187 mg, 42%. ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.56 (bs, 0.25H), 6.42 (bs, 0.75H), 4.60-4.47 (m, 0.25H), 4.41 (t, J = 7.8 Hz, 0.75H), 4.01-3.47 (m, 4H), 2.47-2.31 (m, 2H), 1.99-1.57 (m, 2H), 1.44-1.14 (m, 14H), 1.02-0.88 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, major rotamer): δ 171.5, 156.1, 95.8, 73.4, 62.3, 59.1, 51.6, 49.9, 30.3, 28.4, 19.5, 13.8, 12.70, 12.65; HRMS (ESI): m/z $[M+H]^+$ for $C_{16}H_{29}N_2O_3^+$ calcd. 297.2173; found 297.2175.



79c

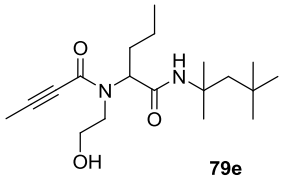
***N*-(1-(cyclohexylamino)-1-oxopentan-2-yl)-*N*-(2-hydroxyethyl)pent-2-ynamide** (**79c**): Elution with heptane/EtOAc/MeOH (50:50:1) delivered pure **79c** as a ~ 1:3 mixture of rotamers.[75] Yield: 290 mg, 60%. ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.81 (d, J = 6.7 Hz, 0.25H), 6.56 (d, J = 8.1 Hz, 0.75H), 5.12 (bs, 0.75H), 4.73-4.59 (m, 0.25H), 4.45 (t, J = 7.8 Hz, 0.75H), 4.04-3.39 (m, 5.25H), 2.46-2.30 (m, 2H), 2.20-1.50 (m, 7H), 1.45-1.05 (m, 10H), 1.02-0.89 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, major rotamer): δ 171.3, 156.0, 95.8, 73.4, 62.3, 58.8, 50.2, 48.6, 32.6, 32.5, 30.4, 25.4,

24.7, 19.5, 13.8, 12.71, 12.65; HRMS (EI): m/z $[M]^+$ for $C_{18}H_{30}N_2O_3^{\bullet+}$ calcd. 322.2251; found 322.2276.



79d

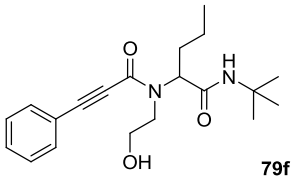
***N*-benzyl-2-(*N*-(2-hydroxyethyl)but-2-ynamido)pentanamide** (**79d**): Elution with heptane/EtOAc/MeOH (60:40:1) delivered pure **79d** as a ~ 1:2 mixture of rotamers.[75] Yield: 237 mg, 50%. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.48-7.11 (m, 5.33H), 6.94 (t, J = 5.5 Hz, 0.67H), 4.86-4.58 (m, 1H), 4.54-4.31 (m, 2.67H), 3.99-3.35 (m, 4.33H), 2.20-2.03 (m, 0.33H), 2.00 (s, 2H), 1.97-1.68 (m, 2.67H), 1.45-1.20 (m, 2H), 1.03-0.88 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 172.2, 170.6, 156.9, 156.1, 138.0, 137.7, 128.68, 128.65, 127.8, 127.6, 127.5, 91.7, 90.7, 73.3, 73.2, 63.0, 62.0, 60.8, 58.9, 50.4, 43.74, 43.69, 31.4, 30.3, 19.6, 19.5, 13.8, 13.7, 4.1, 4.0; HRMS (EI): m/z $[M]^+$ for $C_{18}H_{24}N_2O_3^{\bullet+}$ calcd. 316.1781; found 316.1756.



79e

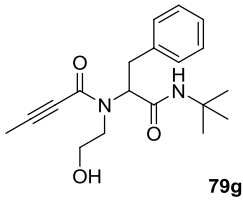
2-(*N*-(2-hydroxyethyl)but-2-ynamido)-*N*-(2,4,4-trimethylpentan-2-yl)pentanamide (**79e**): Elution with heptane/EtOAc/MeOH (60:40:1) delivered pure **79e** as a ~ 3:7 mixture of rotamers.[75] Yield: 239 mg, 47%. ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.55-6.15 (m, 1H), 4.69-4.49 (m, 0.3H), 4.40 (t, J = 7.6 Hz, 0.7H), 4.05-3.40 (m, 4H), 2.02 (s, 3H), 1.97-1.55 (m, 4H), 1.46-1.21 (m, 8H), 1.05-0.90 (m, 12H); ^{13}C NMR (75

MHz, $CDCl_3$, major rotamer): δ 170.9, 156.0, 90.7, 73.3, 62.4, 59.3, 55.7, 52.0, 50.2, 31.6, 31.4, 30.2, 28.7, 28.4, 19.5, 13.8, 4.1; HRMS (EI): m/z $[M]^+$ for $C_{19}H_{34}N_2O_3^{\bullet+}$ calcd. 338.2564; found 338.2597.



79f

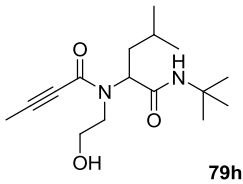
***N*-*tert*-butyl-2-(*N*-(2-hydroxyethyl)-3-phenylpropiolamido)pentanamide** (**79f**): Elution with heptane/EtOAc/MeOH (70:30:1) delivered pure **79f** as a ~ 1:3 mixture of rotamers.[75] Yield: 233 mg, 45%. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.64-7.49 (m, 2H), 7.48-7.30 (m, 3H), 6.68 (bs, 0.25H), 6.37 (bs, 0.75H), 4.99 (bs, 0.75H), 4.65-4.30 (m, 1H), 4.12-3.43 (m, 4.25H), 2.24-2.05 (m, 0.25H), 2.03-1.74 (m, 1.75 H), 1.47-1.21 (m, 11H), 0.98 (t, J = 7.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.4, 169.7, 156.5, 156.0, 132.6, 132.5, 130.5, 130.3, 128.64, 128.59, 120.1, 120.0, 92.0, 91.6, 81.64, 81.56, 63.7, 62.5, 60.9, 59.4, 51.8, 51.6, 50.3, 31.7, 30.4, 28.5, 19.8, 19.6, 13.88, 13.85; HRMS (EI): m/z $[M]^+$ for $C_{20}H_{28}N_2O_3^{\bullet+}$ calcd. 344.2094; found 344.2147.



79g

***N*-(1-(*tert*-butylamino)-1-oxo-3-phenylpropan-2-yl)-*N*-(2-hydroxyethyl)but-2-ynamide** (**79g**): Elution with heptane/EtOAc/MeOH (60:40:1) delivered pure **79g** as a ~ 1:3

mixture of rotamers.[75] Yield: 248 mg, 50%. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.36-7.11 (m, 5H), 6.70 (bs, 0.25H), 6.04 (bs, 0.75H), 4.91 (bs, 0.75H), 4.47 (t, J = 8.0 Hz, 1H), 3.84-3.36 (m, 4.25H), 3.31-3.11 (m, 1.75H), 2.83 (bs, 0.25H), 2.01 (s, 0.75H), 1.99 (s, 2.25H), 1.32 (s, 2.5H), 1.25 (s, 7.5H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.5, 168.9, 156.1, 155.8, 137.6, 136.7, 129.2, 129.1, 128.7, 126.9, 126.8, 91.4, 90.5, 73.7, 73.4, 65.6, 62.0, 61.6, 60.5, 51.7, 51.5, 51.2, 35.9, 34.3, 28.4, 28.3, 4.2, 4.1; HRMS (ESI): m/z $[M+H]^+$ for $C_{19}H_{27}N_2O_3^+$ calcd. 331.2016; found 331.2019.

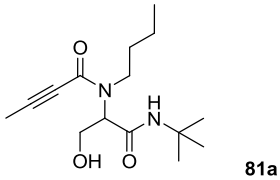


79h

***N-tert*-butyl-2-(*N*-(2-hydroxyethyl)but-2-ynamido)-4-methylpentanamide** (**79h**): Elution with heptane/EtOAc/MeOH (50:50:1) delivered pure **79h** as a ~ 3:7 mixture of rotamers.[75] Yield: 369 mg, 83%. ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.57-6.26 (m, 1H), 4.85-4.44 (m, 1.7H), 4.08-3.40 (m, 4.3H), 2.04 (s, 0.9H), 2.02 (s, 2.1H), 1.97-1.43 (m, 3H), 1.35 (s, 2.7H), 1.33 (s, 6.3H), 1.01-0.89 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.5, 169.7, 156.6, 156.1, 91.3, 90.7, 73.7, 73.4, 73.3, 62.3, 61.5, 61.0, 56.9, 51.60, 51.57, 49.8, 38.1, 36.8, 35.4, 28.5, 28.4, 24.8, 24.6, 23.1, 22.8, 22.3, 21.8, 4.10, 4.09; HRMS (EI): m/z $[M]^+$ for $C_{16}H_{28}N_2O_3^{\bullet+}$ calcd. 296.2094; found 296.2111.

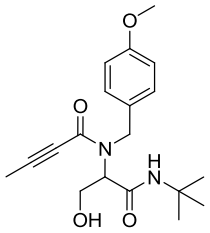
General Procedure for the Synthesis of hydroxypropargylamides 81 through the Ugi reaction

Tetrolic acid (126 mg, 1.5 mmol) was placed in a screw cap vial and dissolved in methanol (2 mL) followed by addition of glycolaldehyde dimer (90 mg, 0.75 mmol), appropriate amine (92 mg, 1.5 mmol) and *tert*-butyl isocyanide (125 mg, 1.5 mmol). The mixture was stirred at room temperature for 24 h. Upon completion of reaction time the resulting mixture was diluted with DCM and evaporated with silica followed by column chromatography delivering pure **81**.



81a

***N*-butyl-*N*-(1-(*tert*-butylamino)-3-hydroxy-1-oxopropan-2-yl)but-2-ynamide** (**81a**): Elution with heptane/EtOAc (50→80%) delivered pure **81a** as a ~ 1:4 mixture of rotamers.[75] Yield: 288 mg, 68%. ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.66 (bs, 0.8H), 6.11 (bs, 0.2H), 4.81-4.72 (m, 0.2H), 4.65 (t, J = 5.9 Hz, 0.8H), 4.22-4.10 (m, 0.2H), 4.09-3.96 (m, 0.8), 3.96-3.53 (m, 3.6H), 3.52-3.39 (m, 0.2H), 3.17-3.03 (m, 0.2H), 2.04 (s, 2.4H), 2.02 (s, 0.6H), 1.75-1.43 (m, 2H), 1.42-1.22 (m, 11H), 1.00-0.83 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 169.5, 169.2, 156.2, 156.0, 90.5, 90.3, 73.2, 63.3, 61.7, 60.8, 58.7, 51.8, 51.3, 48.1, 44.8, 31.7, 30.4, 28.52, 28.49, 20.4, 20.0, 13.63, 13.55, 4.1, 4.0; HRMS (ESI): m/z $[M+H]^+$ for $C_{15}H_{27}N_2O_3^+$ calcd. 283.2016; found 283.2016.



81b

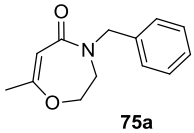
***N*-(1-(*tert*-butylamino)-3-hydroxy-1-oxopropan-2-yl)-*N*-(4-methoxybenzyl)but-2-ynamide** (**81b**): Elution with heptane/EtOAc (50→80%) delivered pure **81b** as a ~ 1:2 mixture of rotamers.[75] Yield: 208 mg, 40%. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.37-7.23 (m, 2H), 6.96-6.80 (m, 2H), 6.07 (bs, 0.67H), 5.34 (bs, 0.33H), 5.13 (bd, J = 14.4 Hz, 0.33H), 4.98 (d, J = 15.6 Hz, 0.67H), 4.72 (d, J = 15.6 Hz, 0.67H), 4.53-4.19 (m, 1.33H), 4.10-3.91 (m, 1H), 3.80 (s, 2H), 3.79 (s, 1H), 3.75-3.61 (m, 1H), 3.52 (bs, 0.67H), 3.36 (bs, 0.33H), 2.04 (s, 2H), 1.99 (s, 1H), 1.19 (s, 6H), 1.15 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 169.0, 168.7, 159.5, 155.9, 130.0, 129.4, 129.1, 128.7, 114.5, 114.4, 91.4, 91.2, 73.4, 73.3, 62.9, 61.7, 60.9, 59.6, 55.3, 52.2, 51.5, 51.3, 35.4, 28.5, 28.2, 4.12, 4.09; HRMS (ESI): m/z $[M+H]^+$ for $C_{19}H_{27}N_2O_4^+$ calcd. 347.1965; found 347.1960.

General procedure for the gold-catalyzed cycloisomerization of hydroxypropargylamides 74, 79 and 81 into oxazepines 75 (Conditions A)

Hydroxypropargylamide **74, 79** or **81** (0.3 mmol) was dissolved in dry $CHCl_3$ (1.2 mL) followed by addition of $Au(PPh_3)Cl$ (7.4 mg, 0.015 mmol) and AgOTf (3.9 mg, 0.015 mmol). The resulting mixture was stirred at rt for 2-4 h in a sealed screw cap vial. The resulting mixture was concentrated under reduced pressure and loaded onto a silica gel column delivering pure **75**.

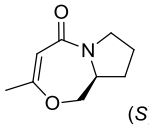
General procedure for the silver-catalyzed cycloisomerization of hydroxypropargylamides 74, 79 and 81 into oxazepines 75 (Conditions B)

Hydroxypropargylamide **74, 79** or **81** (0.3 mmol) was dissolved in dry $CHCl_3$ (1.2 mL) followed by addition of AgOTf (3.9 mg, 0.015 mmol). The resulting mixture was stirred at 50 °C for 15 h in a sealed screw cap vial. The resulting mixture was concentrated under reduced pressure and loaded onto a silica gel column delivering pure **75**.



75a

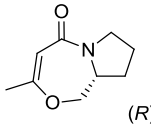
4-Benzyl-7-methyl-3,4-dihydro-1,4-oxazepin-5(2*H*)-one (**75a**): Elution with heptane/EtOAc (50→70%) provided pure **75a**. Yield: 62.6 mg, 96% (procedure A); 59.3 mg, 91% (procedure B). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.40-7.12 (m, 5H), 5.21 (s, 1H), 4.63 (s, 2H), 4.22-4.03 (m, 2H), 3.52-3.33 (m, 2H), 1.93 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 166.6, 160.3, 137.0, 128.7, 128.0, 127.5, 99.1, 71.4, 51.4, 47.9, 22.6; HRMS (EI): m/z $[M]^+$ for $C_{13}H_{15}NO_2^{\bullet+}$ calcd. 217.1097; found 217.1122.



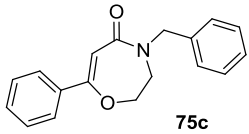
(*S*)-**75b**

(*S*)-3-methyl-7,8,9,9a-tetrahydropyrrolo[2,1-*c*][1,4]oxazepin-5(1*H*)-one ((*S*)-**75b**): Elution with pure EtOAc provided pure (*S*)-**75b**. Yield: 47.7 mg, 95% (procedure A); 44.6 mg, 89% (procedure B). $[\alpha]_D^{20}$ = –80.1 (c = 1, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.10 (s, 1H), 4.39

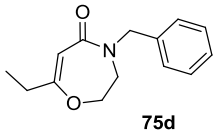
(d, J = 11.7 Hz, 1H), 3.92-3.63 (m, 3H), 3.53-3.39 (m, 2H), 2.26-2.12 (m, 2H), 2.07-1.73 (m, 5H), 1.67-1.49 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 164.3, 161.1, 99.0, 74.2, 57.6, 47.3, 29.7, 22.8, 22.7; HRMS (EI): m/z $[M]^+$ for $C_{13}H_{15}NO_2^{\bullet+}$ calcd. 167.0941; found 167.0942.


(*R*)-**75b**

(*R*)-3-methyl-7,8,9,9a-tetrahydropyrrolo[2,1-*c*][1,4]oxazepin-5(1*H*)-one ((*R*)-**75b**): Elution with pure EtOAc provided pure (*R*)-**75b**. Yield: 48.2 mg, 96% (procedure A). $[\alpha]_D^{20}$ = + 81.8 (c = 0.6, $CHCl_3$).

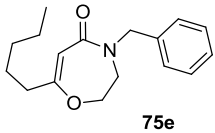

75c

4-benzyl-7-phenyl-3,4-dihydro-1,4-oxazepin-5(2*H*)-one (**75c**): Elution with heptane/EtOAc (30%) provided pure **75c**. Yield: 61.2 mg, 73% (procedure A); 62.0 mg, 74% (procedure B). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.71-7.60 (m, 2H), 7.45-7.21 (m, 8H), 5.93 (s, 1H), 4.72 (s, 2H), 4.45-4.33 (m, 2H), 3.63-3.52 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 166.7, 159.1, 136.9, 135.5, 130.1, 128.8, 128.4, 128.1, 127.6, 126.6, 98.8, 71.7, 51.7, 48.2; HRMS (EI): m/z $[M]^+$ for $C_{18}H_{17}NO_2^{\bullet+}$ calcd. 279.1254; found 279.1262.



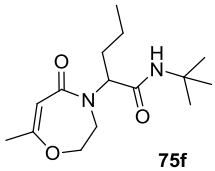
75d

4-benzyl-7-ethyl-3,4-dihydro-1,4-oxazepin-5(2*H*)-one (**75d**): Elution with heptane/EtOAc (40%) provided pure **75d**. Yield: 58.3 mg, 84% (procedure A); 59.7 mg, 86% (procedure B). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.40-7.18 (m, 5H), 5.22 (s, 1H), 4.65 (s, 2H), 4.22-4.10 (m, 2H), 3.50-3.38 (m, 2H), 2.20 (q, J = 7.5 Hz, 2H), 1.11 (t, J = 7.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 166.9, 164.9, 137.1, 128.7, 128.1, 127.5, 97.7, 71.4, 51.5, 48.0, 29.6, 12.1; HRMS (EI): m/z $[M]^+$ for $C_{14}H_{17}NO_2^{\bullet+}$ calcd. 231.1254; found 231.1244.



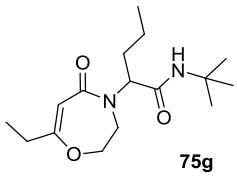
75e

4-benzyl-7-pentyl-3,4-dihydro-1,4-oxazepin-5(2*H*)-one (**75e**): Elution with heptane/EtOAc (40%) provided pure **75e**. Yield: 73.8 mg, 90% (procedure A); 70.5 mg, 86% (procedure B). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.38-7.18 (m, 5H), 5.22 (s, 1H), 4.65 (s, 2H), 4.22-4.08 (m, 2H), 3.49-3.37 (m, 2H), 2.23-2.08 (m, 2H), 1.61-1.45 (m, 2H), 1.41-1.18 (m, 4H), 0.89 (t, J = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 166.8, 163.8, 137.1, 128.7, 128.1, 127.5, 98.6, 71.4, 51.4, 48.0, 36.5, 31.2, 27.3, 22.4, 14.0; HRMS (EI): m/z $[M]^+$ for $C_{17}H_{23}NO_2^{\bullet+}$ calcd. 273.1723; found 273.1691.



75f

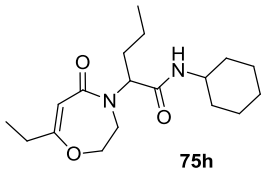
***N-tert*-butyl-2-(7-methyl-5-oxo-2,3-dihydro-1,4-oxazepin-4(5*H*)-yl)pentanamide** (**75f**): Elution with heptane/EtOAc (50%) provided pure **75f**. Yield: 75.3 mg, 89% (procedure A); 75.4 mg, 89% (procedure B). ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.99 (bs, 1H), 5.15 (s, 1H), 4.89 (t, J = 7.7 Hz, 1H), 4.37 (dd, J = 12.4, 6.3 Hz, 1H), 4.06 (dd, J = 12.4, 6.7 Hz, 1H), 3.68 (dd, J = 15.9, 6.3 Hz, 1H), 3.47 (dd, J = 15.9, 6.7 Hz, 1H), 1.95 (s, 3H), 1.91-1.71 (m, 1H), 1.65-1.45 (m, 1H), 1.39-1.17 (m, 11H), 0.92 (t, J = 7.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 169.8, 167.3, 160.7, 98.6, 72.0, 56.7, 51.2, 43.8, 30.2, 28.7, 22.6, 19.2, 13.9; HRMS (ESI): m/z $[M+H]^+$ for $C_{15}H_{27}N_2O_3^+$ calcd. 283.2016; found 283.2020.



75g

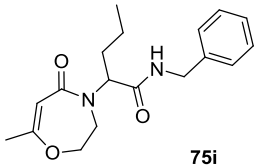
***N-tert*-butyl-2-(7-ethyl-5-oxo-2,3-dihydro-1,4-oxazepin-4(5*H*)-yl)pentanamide** (**75g**): Elution with heptane/EtOAc (40%) provided pure **75g**. Yield: 66.7 mg, 75% (procedure A); 56.9 mg, 64% (procedure B). ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.99 (bs, 1H), 5.14 (s, 1H), 4.90 (t, J = 7.7 Hz, 1H), 4.38 (dd, J = 12.4, 6.3 Hz, 1H), 4.05 (dd, J = 12.4, 6.6 Hz, 1H), 3.68 (dd, J = 15.9, 6.3 Hz, 1H), 3.46 (dd, J = 15.9, 6.6 Hz, 1H), 2.21 (q, J = 7.5 Hz, 2H), 1.90-1.71 (m, 1H), 1.65-1.47 (m, 1H), 1.36-1.19 (m, 11H), 1.12 (t, J = 7.5 Hz, 3H), 0.93 (t, J = 7.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 169.8, 167.6, 165.3, 97.1, 71.9,

56.7, 51.2, 43.9, 30.2, 29.6, 28.7, 19.2, 13.9, 12.0; HRMS (ESI): m/z $[M+H]^+$ for $C_{16}H_{29}N_2O_3^+$ calcd. 297.2173; found 297.2175.



75h

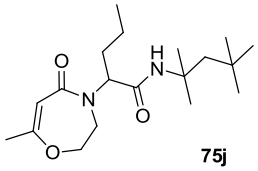
***N*-cyclohexyl-2-(7-ethyl-5-oxo-2,3-dihydro-1,4-oxazepin-4(5*H*)-yl)pentanamide** (**75h**): Elution with heptane/EtOAc (40%) provided pure **75h**. Yield: 74.5 mg, 77% (procedure A); 71.6 mg, 74% (procedure B). ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.12 (bd, J = 8.1 Hz, 1H), 5.14 (s, 1H), 4.98 (dd, J = 8.3, 7.2 Hz, 1H), 4.38 (dd, J = 12.4, 6.3 Hz, 1H), 4.07 (dd, J = 12.4, 6.6 Hz, 1H), 3.78-3.58 (m, 2H), 3.47 (dd, J = 15.9, 6.6 Hz, 1H), 2.20 (q, J = 7.5 Hz, 2H), 1.93-1.51 (m, 7H), 1.43-1.01 (m, 10H), 0.93 (t, J = 7.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 169.6, 167.7, 165.4, 97.1, 71.9, 56.3, 48.1, 44.0, 33.0, 32.8, 30.4, 29.6, 25.5, 24.8, 24.7, 19.2, 13.9, 12.1; HRMS (EI): m/z $[M]^+$ for $C_{18}H_{30}N_2O_3^{\bullet+}$ calcd. 322.2251; found 322.2276.



75i

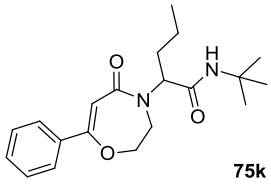
***N*-benzyl-2-(7-methyl-5-oxo-2,3-dihydro-1,4-oxazepin-4(5*H*)-yl)pentanamide** (**75i**): Elution with heptane/EtOAc (40%) provided pure **75i**. Yield: 83.5 mg, 88% (procedure A); 77.8 mg, 82% (procedure B). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.37-7.18 (m, 5H), 6.94 (t, J = 5.6 Hz, 1H), 5.12-5.01 (m, 2H), 4.37 (d, J = 6.0 Hz, 2H), 4.26 (dd, J = 12.4, 6.3 Hz, 1H), 3.95 (dd, J = 12.4, 6.6 Hz, 1H), 3.65 (dd, J = 15.9,

6.3 Hz, 1H), 3.47 (dd, J = 15.9, 6.6 Hz, 1H), 1.95-1.76 (m, 4H), 1.71-1.52 (m, 1H), 1.38-1.18 (m, 2H), 0.92 (t, J = 7.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.6, 167.4, 160.8, 138.3, 128.6, 127.7, 127.4, 98.4, 71.8, 56.2, 43.9, 43.3, 30.5, 22.6, 19.2, 13.9; HRMS (EI): m/z $[M]^+$ for $C_{18}H_{24}N_2O_3^{\bullet+}$ calcd. 316.1781; found 316.1788.



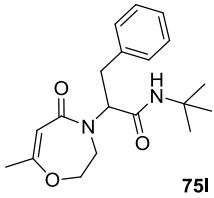
75j

2-(7-methyl-5-oxo-2,3-dihydro-1,4-oxazepin-4(5*H*)-yl)-*N*-(2,4,4-trimethylpentan-2-yl)pentanamide (**75j**): Elution with heptane/EtOAc (30%) provided pure **75j**. Yield: 88.3 mg, 87% (procedure A); 85.3 mg, 84% (procedure B). ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.01 (bs, 1H), 5.14 (s, 1H), 4.87 (t, J = 7.7 Hz, 1H), 4.33 (dd, J = 12.4, 6.3 Hz, 1H), 4.12 (dd, J = 12.4, 6.5 Hz, 1H), 3.64 (dd, J = 15.9, 6.3 Hz, 1H), 3.49 (dd, J = 15.9, 6.5 Hz, 1H), 1.94 (s, 3H), 1.89-1.70 (m, 2H), 1.68-1.45 (m, 2H), 1.41-1.14 (m, 8H), 0.98 (s, 9H), 0.92 (t, J = 7.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 169.4, 167.2, 160.6, 98.6, 71.9, 57.0, 55.2, 51.7, 43.8, 31.6, 31.4, 30.2, 29.1, 29.0, 22.6, 19.3, 13.9; HRMS (EI): m/z $[M]^+$ for $C_{19}H_{34}N_2O_3^{\bullet+}$ calcd. 338.2564; found 338.2547.



75k

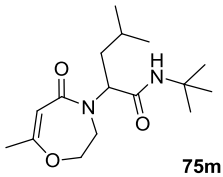
***N-tert*-butyl-2-(5-oxo-7-phenyl-2,3-dihydro-1,4-oxazepin-4(5*H*)-yl)pentanamide** (**75k**): Elution with heptane/EtOAc (40%) provided pure **75k**. Yield: 92.0 mg, 89% (procedure A); 80.6 mg, 78% (procedure B). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.71-7.62 (m, 2H), 7.46-7.32 (m, 3H), 6.06 (bs, 1H), 5.84 (s, 1H), 4.96 (t, J = 7.7 Hz, 1H), 4.62 (dd, J = 12.4, 6.3 Hz, 1H), 4.27 (dd, J = 12.4, 6.7 Hz, 1H), 3.82 (dd, J = 15.9, 6.3 Hz, 1H), 3.60 (dd, J = 15.9, 6.7 Hz, 1H), 1.94-1.75 (m, 1H), 1.70-1.51 (m, 1H), 1.41-1.21 (m, 11H), 0.95 (t, J = 7.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 169.7, 167.3, 159.3, 135.4, 130.1, 128.4, 126.5, 98.2, 72.3, 56.9, 51.3, 44.1, 30.3, 28.7, 19.3, 13.9; HRMS (EI): m/z $[M]^+$ for $C_{20}H_{28}N_2O_3^{\bullet+}$ calcd. 344.2094; found 344.2125.



75l

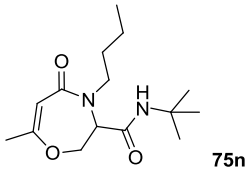
***N-tert*-butyl-2-(7-methyl-5-oxo-2,3-dihydro-1,4-oxazepin-4(5*H*)-yl)-3-phenylpropanamide** (**75l**): Elution with heptane/EtOAc (50%) provided pure **75l**. Yield: 83.3 mg, 84% (procedure A); 85.2 mg, 86% (procedure B). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.36-7.10 (m, 5H), 5.95 (bs, 1H), 5.25 (t, J = 8.2 Hz, 1H), 5.08 (s, 1H), 4.12-3.90 (m, 2H), 3.77-3.62 (m, 1H), 3.55-3.42 (m, 1H), 3.21 (dd, *J* = 14.4, 7.8 Hz, 1H), 2.94 (dd, *J* = 14.4, 8.5 Hz, 1H), 1.89 (s, 3H), 1.26 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 169.2, 167.3, 160.8, 136.9, 129.0, 128.6, 126.7,

98.4, 71.8, 57.7, 51.2, 44.1, 34.5, 28.6, 22.6; HRMS (EI): m/z $[M]^+$ for $C_{19}H_{26}N_2O_3^{\bullet+}$ calcd. 330.1938; found 330.1948.



75m

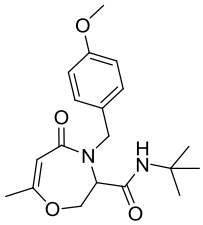
***N-tert*-butyl-4-methyl-2-(7-methyl-5-oxo-2,3-dihydro-1,4-oxazepin-4(5*H*)-yl)pentanamide** (**75m**): Elution with heptane/EtOAc (50%) provided pure **75m**. Yield: 84.5 mg, 95% (procedure A); 75.6 mg, 85% (procedure B). ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.02 (bs, 1H), 5.14 (s, 1H), 4.98 (dd, J = 8.5, 6.7 Hz, 1H), 4.37 (dd, J = 12.4, 6.3 Hz, 1H), 4.03 (dd, J = 12.4, 6.6 Hz, 1H), 3.67 (dd, J = 15.9, 6.3 Hz, 1H), 3.45 (dd, J = 15.9, 6.6 Hz, 1H), 1.94 (s, 3H), 1.70-1.35 (m, 3H), 1.30 (s, 9H), 0.92 (d, J = 6.5 Hz, 3H), 0.90 (d, J = 6.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 169.8, 167.2, 160.6, 98.6, 71.9, 55.1, 51.1, 43.8, 36.8, 28.6, 25.0, 23.1, 22.5, 22.2; HRMS (ESI): m/z $[M+H]^+$ for $C_{16}H_{29}N_2O_3^+$ calcd. 297.2173; found 297.2180.



75n

***N-tert*-butyl-4-butyl-7-methyl-5-oxo-2,3,4,5-tetrahydro-1,4-oxazepine-3-carboxamide** (**75n**): Elution with heptane/EtOAc (50%) provided pure **75n**. Yield: 69.5 mg, 82% (procedure A); 75.4 mg, 89% (procedure B). ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.86 (bs, 1H), 5.17 (s, 1H), 5.01 (dd, J = 12.0, 5.4 Hz, 1H), 4.06 (d, J = 5.4 Hz, 1H), 3.98 (d, J = 12.0 Hz, 1H), 3.69-3.52 (m, 1H), 3.31-3.16 (m, 1H), 1.92 (s, 3H),

1.65-1.20 (m, 13H), 0.93 (t, J = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 166.3, 165.5, 162.6, 99.2, 71.5, 64.6, 51.7, 49.3, 29.6, 28.6, 21.9, 20.2, 13.8; HRMS (ESI): m/z $[M+H]^+$ for $C_{15}H_{27}N_2O_3^+$ calcd. 283.2016; found 283.2019.

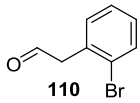


75o

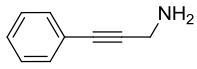
***N-tert*-butyl-4-(4-methoxybenzyl)-7-methyl-5-oxo-2,3,4,5-tetrahydro-1,4-oxazepine-3-carboxamide** (**75o**): Elution with heptane/EtOAc (50%) provided pure **75o**. Yield: 85.2 mg, 82% (procedure A); 82.1 mg, 79% (procedure B). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.24 (d, J = 8.6 Hz, 2H), 6.85 (d, J = 8.6 Hz, 2H), 5.62 (bs, 1H), 5.23 (s, 1H), 4.92 (dd, J = 12.0, 5.4 Hz, 1H), 4.66 (d, J = 14.3 Hz, 1H), 4.54 (d, J = 14.3 Hz, 1H), 4.08 (d, J = 5.4 Hz, 1H), 3.85 (d, J = 12.0 Hz, 1H), 3.79 (s, 3H), 1.91 (s, 3H), 1.18 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 165.8, 165.7, 162.9, 159.5, 130.2, 128.6, 114.4, 98.9, 71.6, 63.5, 55.3, 51.9, 51.5, 28.3, 22.0; HRMS (ESI): m/z $[M+H]^+$ for $C_{19}H_{27}N_2O_4^+$ calcd. 347.1965; found 347.1966.

Chapter 4

Synthesis of starting materials

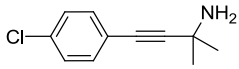


110



111b

2-Bromophenylacetaldehyde (**110**)[54f] and 3-phenylpropargylamine (**111b**)[76] were synthesized following known procedures.

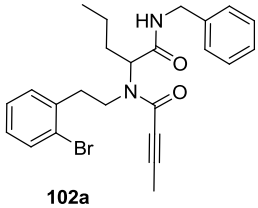


111a

4-(4-Chlorophenyl)-2-methylbut-3-yn-2-amine (111a). 1-Chloro-4-iodobenzene (0.715 g, 3 mmol) was placed in a screw cap vial and dissolved in THF (5 mL) followed by addition of 2-methylbut-3-yn-2-amine (0.299 g, 3.6 mmol), $Pd(PPh_3)_2Cl_2$ (63 mg, 0.09 mmol), CuI (29 mg, 0.15 mmol) and triethylamine (1 mL). The vial was several times evacuated and backfilled with argon. The sealed reaction mixture was heated with a stirring at 80 °C for 18.5 h. The resulting mixture was diluted with EtOAc (30 mL). The solids were filtered off and the filtrate was evaporated with silica followed by column chromatography with EtOAc-MeOH (1-3%) as eluent delivering pure product. Yield: 230 mg, 40%. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.30 (d, J = 8.3 Hz, 2H), 7.24 (d, J = 8.3 Hz, 2H), 1.80 (bs, 2H), 1.48 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 133.8, 132.7, 128.5, 121.9, 79.0, 45.8, 31.8.

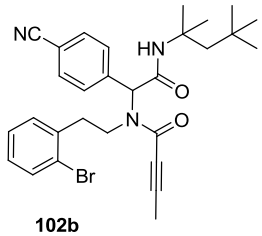
Synthesis of propargylamides 102a-g,i through the Ugi reaction

3-Substituted propiolic acid **39** (0.5 mmol) was dissolved in methanol (2 mL) followed by addition of appropriate 2-bromophenethylamine **96** (0.5 mmol), aldehyde **2** (0.5 mmol) and isocyanide **4** (0.5 mmol). The reaction mixture was stirred at rt for 24 h in a sealed screw cap vial. The resulting mixture was concentrated and subjected to the column chromatography on silicagel with heptane-EtOAc (15-40%) as eluent to give the desired propargylamides **102a-g,i**.



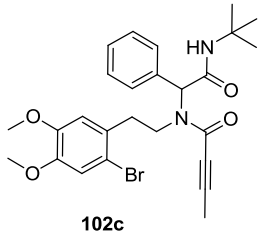
102a

***N*-benzyl-2-(*N*-(2-bromophenethyl)but-2-ynamido)pentanamide (102a).** Mixture of rotamers ~ 4:1.[75] Yield: 200 mg, 88%. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.60-7.42 (m, 1H), 7.39-6.97 (m, 9H), 5.03-4.74 (m, 1H), 4.58-4.28 (m, 2H), 4.02-3.80 (m, 0.8H), 3.74-3.48 (m, 1H), 3.38-3.19 (m, 0.2H), 3.17-2.85 (m, 2H), 2.34-1.55 (m, 5H), 1.49-1.12 (m, 2H), 1.06-0.80 (m, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz, major rotamer): δ 170.4, 156.1, 138.2, 138.0, 132.8, 131.2, 128.6, 128.4, 127.8, 127.7, 127.3, 124.5, 90.3, 73.4, 57.3, 46.4, 43.5, 36.3, 30.4, 19.4, 13.9, 4.4; HRMS (EI, $[M]^+$) for $C_{24}H_{27}BrN_2O_2^{\bullet+}$ calcd. 454.1250, found 454.1239.



102b

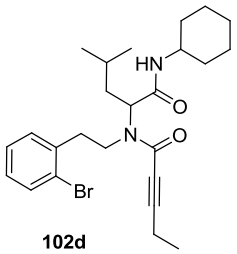
***N*-(2-bromophenethyl)-*N*-(1-(4-cyanophenyl)-2-oxo-2-(2,4,4-trimethylpentan-2-ylamino)ethyl)but-2-ynamide (102b).** Mixture of rotamers ~ 17:3.[75] Yield: 244 mg, 91%. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.74-7.33 (m, 5H), 7.26-6.95 (m, 3H), 6.33 (s, 0.85H), 6.11 (s, 0.15H), 5.92 (s, 0.85H), 5.77 (s, 0.15H), 3.94-3.73 (m, 1.7H), 3.73-3.57 (m, 0.15H), 3.44-3.24 (m, 0.15H), 3.09-2.67 (m, 1.85H), 2.56-2.38 (m, 0.15H), 2.04 (s, 3H), 1.77 (s, 0.3H), 1.72 (s, 1.7H), 1.47 (s, 0.9H), 1.44 (s, 5.1H), 1.01 (s, 1.35H), 0.95 (s, 7.65H); ^{13}C NMR (75 MHz, $CDCl_3$, major rotamer): δ 166.8, 155.8, 140.5, 137.7, 132.8, 132.5, 131.0, 129.8, 128.5, 127.8, 124.3, 118.4, 112.3, 91.0, 73.2, 61.9, 56.0, 52.1, 48.0, 36.4, 31.6, 31.4, 28.7, 28.6, 4.5; MS (CI): m/z (relative intensity) 536 ([M+H]$^+$, 100), 407 (52), 380 (24).



102c

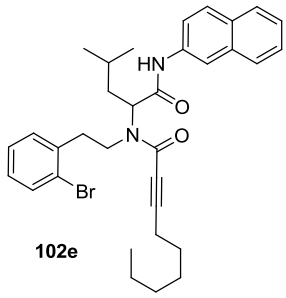
***N*-(2-bromo-4,5-dimethoxyphenethyl)-*N*-(2-(*tert*-butylamino)-2-oxo-1-phenylethyl)but-2-ynamide (102c).** Mixture of rotamers ~ 17:3.[75] Yield: 239 mg, 93%. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.59-7.30 (m, 5H), 6.88 (s, 0.85H), 6.83 (s, 0.15H), 6.51 (s, 0.15H), 6.29 (s, 0.85H), 6.05 (s, 0.15H), 6.00-5.82 (m, 1.7H), 5.61 (bs, 0.15H), 3.92-

3.52 (m, 7.85H), 3.38-3.19 (m, 0.15H), 3.01-2.76 (m, 1H), 2.47-2.19 (m, 1H), 2.06 (s, 0.45H), 2.01 (s, 2.55H), 1.40 (s, 1.35H), 1.35 (s, 7.65H); ^{13}C NMR (75 MHz, $CDCl_3$, major rotamer): δ 168.3, 155.7, 148.3, 148.1, 135.1, 130.2, 129.8, 128.9, 128.6, 115.2, 113.8, 113.6, 89.5, 73.6, 61.8, 56.1, 56.0, 51.7, 47.3, 36.1, 28.6, 4.5; HRMS (EI, $[M]^+$) for $C_{26}H_{31}BrN_2O_4^{\bullet+}$ calcd. 514.1462, found 514.1457.



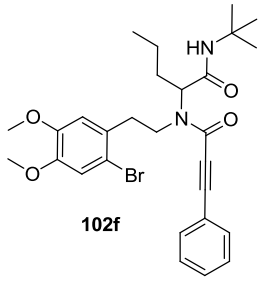
102d

***N*-(2-bromophenethyl)-*N*-(1-(cyclohexylamino)-4-methyl-1-oxopentan-2-yl)pent-2-ynamide (102d).** Mixture of rotamers ~ 4:1.[75] Yield: 220 mg, 93%. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.58-7.47 (m, 1H), 7.39-7.18 (m, 2H), 7.16-7.01 (m, 1H), 6.58 (bd, J = 8.0 Hz, 0.8H), 5.90 (bd, J = 8.0 Hz, 0.2H), 5.08-4.73 (m, 1H), 4.03-3.84 (m, 0.8H), 3.84-3.47 (m, 2H), 3.42-3.24 (m, 0.2H), 3.20-2.84 (m, 2H), 2.50-2.30 (m, 2H), 2.03-0.72 (m, 22H); ^{13}C NMR (75 MHz, $CDCl_3$, major rotamer): δ 169.6, 156.1, 138.0, 132.8, 131.1, 128.4, 127.7, 124.4, 95.3, 73.4, 55.4, 48.2, 46.3, 36.7, 36.2, 32.7, 32.6, 25.5, 24.8, 24.7, 24.6, 22.8, 22.4, 12.9, 12.7; HRMS (EI, $[M]^+$) for $C_{25}H_{35}BrN_2O_2^{\bullet+}$ calcd. 474.1876, found 474.1871.



102e

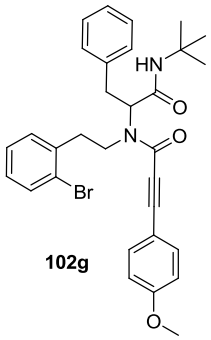
***N*-(2-bromophenethyl)-*N*-(4-methyl-1-(naphthalen-2-ylamino)-1-oxopentan-2-yl)non-2-ynamide (102e).** Mixture of rotamers ~ 9:1.[75] Yield: 247 mg, 86%. ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.37 (bs, 0.9H), 8.78 (bs, 0.1H), 8.37-8.26 (m, 1H), 7.84-6.93 (m, 10H), 5.29-5.21 (m, 0.1H), 5.20-5.01 (m, 0.9H), 4.14-3.94 (m, 0.9H), 3.83-3.63 (m, 1H), 3.54-3.35 (m, 0.1H), 3.30-2.90 (m, 2H), 2.40-0.65 (m, 22H); ^{13}C NMR (75 MHz, $CDCl_3$, major rotamer): δ 169.2, 156.8, 137.6, 135.6, 133.8, 132.8, 131.2, 130.6, 128.6, 128.4, 127.68, 127.66, 127.5, 126.4, 124.9, 124.5, 120.1, 116.5, 95.4, 73.7, 56.9, 46.6, 36.7, 36.1, 31.2, 28.7, 27.6, 24.9, 22.69, 22.66, 22.4, 19.3, 14.0; HRMS (EI, $[M]^+$) for $C_{33}H_{39}BrN_2O_2^{\bullet+}$ calcd. 574.2189, found 574.2217.



102f

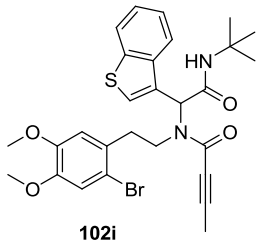
2-(*N*-(2-bromo-4,5-dimethoxyphenethyl)-3-phenylpropiolamido)-*N*-*tert*-butylpentanamide (102f). Mixture of rotamers ~ 4:1.[75] Yield: 217 mg, 80%. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.62-7.52 (m, 2H), 7.49-7.32 (m, 3H), 6.99 (s, 0.2H), 6.94 (s, 0.8H), 6.90 (s, 0.2H), 6.72 (s,

0.8H), 6.34 (bs, 0.8H), 5.62 (bs, 0.2H), 4.80 (t, J = 7.6 Hz, 1H), 4.08-3.33 (m, 8H), 3.20-2.78 (m, 2H), 2.23-1.96 (m, 1H), 1.90-1.64 (m, 1H), 1.48-1.18 (m, 11H), 1.06-0.92 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, major rotamer): δ 169.5, 155.9, 148.6, 148.4, 132.4, 130.3, 129.9, 128.6, 120.3, 115.5, 114.2, 113.4, 91.0, 81.8, 57.7, 56.1, 55.8, 51.3, 46.5, 36.5, 30.2, 28.6, 19.4, 13.9; HRMS (EI, $[M]^+$) for $C_{28}H_{35}BrN_2O_4^{\bullet+}$ calcd. 542.1775, found 542.1796.



102g

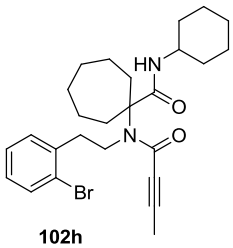
***N*-(2-bromophenethyl)-*N*-(1-(*tert*-butylamino)-1-oxo-3-phenylpropan-2-yl)-3-(4-methoxyphenyl)propiolamide (102g).** Mixture of rotamers ~ 21:4.[75] Yield: 121 mg, 43%. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.60-6.98 (m, 11H), 6.95-6.78 (m, 2H), 6.46 (bs, 0.84H), 5.61 (bs, 0.16H), 5.11-4.81 (m, 1H), 4.02-2.84 (m, 9H), 1.32 (s, 7.56H), 1.29 (s, 1.44H); ^{13}C NMR (75 MHz, $CDCl_3$, major rotamer): δ 169.0, 161.2, 156.3, 138.0, 137.0, 134.4, 132.9, 131.1, 129.1, 128.6, 128.4, 127.7, 126.7, 124.5, 114.2, 112.0, 91.9, 80.9, 60.2, 55.4, 51.3, 47.4, 36.4, 34.3, 28.5; HRMS (ESI, $[M+H]^+$) for $C_{31}H_{34}BrN_2O_3^+$ calcd. 561.1747, found 561.1756.



102i

***N*-(1-(benzo[*b*]thiophen-3-yl)-2-(*tert*-butylamino)-2-oxoethyl)-*N*-(2-bromo-4,5-dimethoxyphenethyl)but-2-ynamide (102i).** Mixture of rotamers ~ 9:1.[75] Yield: 203 mg, 71%. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.01 (s, 0.9H), 7.94-7.83 (m, 1H), 7.80-7.61 (m, 1.1H), 7.47-7.30 (m, 2H), 6.82 (s, 0.9H), 6.70 (s, 0.1H), 6.40 (s, 1H), 6.32 (s, 0.1H), 6.16 (s, 0.9H), 6.07 (bs, 0.9H), 5.65 (bs, 0.1H), 3.87-3.56 (m, 7.9H), 3.46-3.30 (m, 0.1H), 2.93-2.63 (m, 1H), 2.18-1.89 (m, 4H), 1.41 (s, 0.9H), 1.38 (s, 8.1H); ^{13}C NMR (75 MHz, $CDCl_3$, major rotamer): δ 168.0, 155.8, 148.3, 148.1, 139.5, 138.5, 130.1, 129.5, 128.0, 125.2, 125.0, 122.9, 121.6, 115.2, 113.7, 113.4, 90.0, 73.5, 56.1, 54.4, 51.8, 46.7, 36.1, 28.6, 4.6; HRMS (EI, $[M]^+$) for $C_{28}H_{31}BrN_2O_4S^{\bullet+}$ calcd. 570.1182, found 570.1207.

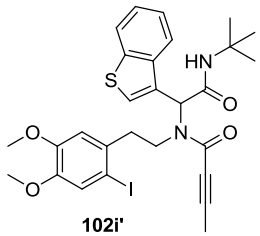
Synthesis of 1-(*N*-(2-bromophenethyl)but-2-ynamido)-*N*-cyclohexylcycloheptanecarbox-amide (102h) through the Ugi reaction



102h

Tetrolic acid (**39a**) (42 mg, 0.5 mmol) was dissolved in methanol (2 mL) followed by addition of 2-bromophenethylamine (**96a**) (100 mg, 0.5 mmol), cycloheptanone (**109**) (56 mg, 0.5 mmol) and cyclohexyl isocyanide (**4b**) (55 mg, 0.5 mmol). The reaction mixture was stirred at rt for 2 h and then heated at 70 °C for 72 h in a sealed screw cap vial. The resulting mixture was concentrated and subjected to the column chromatography on silicagel with heptane-EtOAc (40%) as eluent to give the desired propargylamide **102h**. Mixture of rotamers ~ 3:1.[75] Yield: 85 mg, 35%. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.61-7.48 (m, 1H), 7.33-7.19 (m, 2H), 7.18-7.03 (m, 1H), 5.96-5.59 (m, 1H), 3.96-3.63 (m, 2.5H), 3.62-3.50 (m, 0.5H), 3.28-3.10 (m, 1.5H), 3.03-2.93 (m, 0.5H), 2.49-2.31 (m, 1.5H), 2.21-1.01 (m, 23.5H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 173.5, 155.9, 153.5, 138.4, 137.9, 133.0, 131.0, 130.9, 128.5, 128.4, 127.9, 127.7, 124.6, 124.3, 88.2, 83.3, 75.0, 69.3, 48.4, 46.6, 39.4, 38.4, 35.5, 35.2, 32.9, 30.0, 25.7, 24.8, 23.6, 4.3, 3.7; HRMS (ESI, $[M+Na]^+$) for $C_{26}H_{35}BrN_2O_2Na^+$ calcd. 509.1774, found 509.1778.

Synthesis of *N*-(1-(benzo[*b*]thiophen-3-yl)-2-(*tert*-butylamino)-2-oxoethyl)-*N*-(2-iodo-4,5-dimet-hoxyphenethyl)but-2-ynamide (102i') through the Ugi reaction

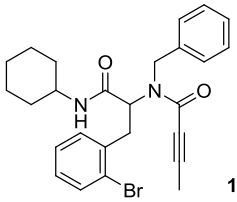


102i'

Tetrolic acid (**39a**) (42 mg, 0.5 mmol) was dissolved in methanol (2 mL) followed by addition of 2-iodo-4,5-dimethoxyphenethylamine (**96b'**) (154 mg, 0.5 mmol), benzothiophene-3-carbaldehyde (**2f**) (81 mg, 0.5 mmol) and *tert*-butyl isocianide (**4a**) (42 mg, 0.5 mmol). The reaction mixture was stirred at rt for 48 h in a sealed screw cap vial. The resulting mixture was concentrated and subjected to the column chromatography on silicagel with heptane-EtOAc (15-25%) as eluent to give the desired propargylamide **102i'**. Mixture of rotamers ~ 9:1.[75] Yield: 142 mg, 46%. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.02 (s, 0.9H), 7.93-7.82 (m, 1H), 7.80-7.62 (m, 1.1H), 7.46-7.31 (m, 2H), 7.03 (s, 0.9H), 6.91 (s, 0.1H), 6.42 (s, 0.1H), 6.38 (s, 0.9H), 6.31 (s, 0.1H), 6.23 (s, 0.9H), 6.06 (bs, 0.9H), 5.65 (bs, 0.1H), 3.92-3.49 (m, 7.9H), 3.45-3.28 (m, 0.1H), 2.90-2.65 (m, 1H), 2.29-2.08 (m, 1.3H), 2.03 (s, 2.7H), 1.41 (s, 0.9H), 1.38 (s, 8.1H); ^{13}C NMR (75 MHz, $CDCl_3$, major rotamer): δ 168.0, 155.8, 149.3, 148.0, 139.6, 138.5, 134.2, 129.3, 128.1, 125.2, 125.0, 123.0, 121.6, 121.4, 112.7, 90.3, 87.3, 73.7, 56.1, 56.0, 54.6, 51.8, 46.9, 40.3, 28.6, 5.0; HRMS (EI, $[M]^+$) for $C_{28}H_{31}IN_2O_4S^{\bullet+}$ calcd. 618.1044, found 618.1040.

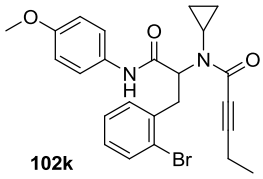
Synthesis of propargylamides 102j-l through the Ugi reaction

3-Substituted propiolic acid **39** (0.5 mmol) was dissolved in methanol (2 mL) followed by addition of amine **3** (0.5 mmol), 2-bromophenylacetaldehyde (**110**) (100 mg, 0.5 mmol) and isocyanide **4** (0.5 mmol). The reaction mixture was stirred at rt for 24 h in a sealed screw cap vial. The resulting mixture was concentrated and subjected to the column chromatography on silicagel with heptane-EtOAc (10-30%) as eluent to give the desired propargylamides **102j-l**.



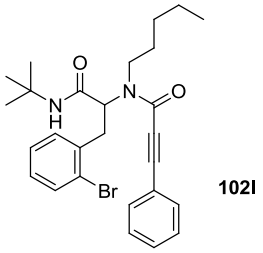
102j

***N*-benzyl-*N*-(3-(2-bromophenyl)-1-(cyclohexylamino)-1-oxopropan-2-yl)but-2-ynamide (102j).** Mixture of rotamers ~ 7:3.[75] Yield: 151 mg, 63%. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.63-7.43 (m, 1H), 7.41-6.98 (m, 8H), 5.85 (bd, J = 6.9 Hz, 0.7H), 5.30-5.08 (m, 0.3H), 5.07-4.77 (m, 1.3H), 4.76-4.59 (m, 0.7H), 4.23 (d, J = 15.7 Hz, 0.7H), 3.80-3.12 (m, 3.3H), 1.98 (s, 3H), 1.82-0.68 (m, 10H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 167.7, 167.5, 155.5, 155.0, 137.3, 137.0, 136.8, 136.7, 132.8, 132.7, 132.3, 131.9, 129.0, 128.9, 128.8, 128.7, 128.4, 128.0, 127.79, 127.76, 127.5, 124.7, 124.6, 91.3, 90.5, 73.6, 73.4, 61.0, 58.7, 52.8, 48.4, 48.0, 36.1, 34.6, 32.54, 32.49, 32.3, 32.2, 25.5, 25.4, 24.56, 24.54, 24.49, 4.2, 4.1; HRMS (EI, $[M]^+$) for $C_{26}H_{29}BrN_2O_2^{\bullet+}$ calcd. 480.1407, found 480.1421.



102k

***N*-(3-(2-bromophenyl)-1-(4-methoxyphenylamino)-1-oxopropan-2-yl)-*N*-cyclopropylpent-2-ynamide (102k).** Yield: 164 mg, 70%. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.71 (s, 1H), 7.62-7.48 (m, 1H), 7.39 (d, J = 8.8 Hz, 2H), 7.34-7.18 (m, 2H), 7.16-7.03 (m, 1H), 6.82 (d, J = 8.8 Hz, 2H), 5.09 (t, J = 7.4 Hz, 1H), 3.76 (s, 3H), 3.68-3.50 (m, 2H), 2.63-2.47 (m, 1H), 2.45-2.29 (m, 2H), 1.19 (t, J = 7.4 Hz, 3H), 1.09-0.74 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 168.1, 158.9, 156.3, 136.9, 133.0, 131.3, 131.1, 128.6, 127.6, 124.9, 121.6, 114.0, 97.6, 74.3, 61.4, 55.5, 34.0, 30.4, 12.84, 12.81, 10.5, 8.3; HRMS (EI, $[M]^+$) for $C_{24}H_{25}BrN_2O_3^{\bullet+}$ calcd. 468.1043, found 468.1041.

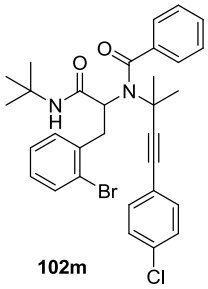


102l

***N*-(3-(2-bromophenyl)-1-(*tert*-butylamino)-1-oxopropan-2-yl)-*N*-pentyl-3-phenylpropiolamide (102l).** Mixture of rotamers ~ 4:1.[75] Yield: 165 mg, 66%. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.60-7.14 (m, 8H), 7.14-6.97 (m, 1H), 6.53 (bs, 0.8H), 5.70 (bs, 0.2H), 5.10-4.82 (m, 1H), 3.72-3.04 (m, 4H), 1.82-1.03 (m, 15H), 1.00-0.71 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, major rotamer): δ 168.6, 155.8, 136.6, 132.9, 132.4, 131.3, 130.3, 128.6, 128.4, 127.5, 124.9, 120.3, 90.8, 81.7, 58.9,

51.3, 48.4, 34.4, 29.3, 29.1, 28.5, 22.3, 14.0; HRMS (EI, $[M]^+$) for $C_{27}H_{33}BrN_2O_2^{\bullet+}$ calcd. 496.1720, found 496.1703.

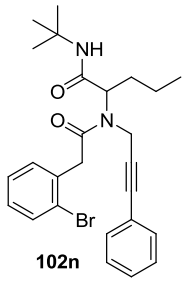
Synthesis of *N*-(3-(2-bromophenyl)-1-(*tert*-butylamino)-1-oxopropan-2-yl)-*N*-(4-(4-chlorophe-nyl)-2-methylbut-3-yn-2-yl)benzamide (102m) through the Ugi reaction



102m

Benzoic acid (**1a**) (61 mg, 0.5 mmol) was dissolved in methanol (2 mL) followed by addition of 4-(4-chlorophenyl)-2-methylbut-3-yn-2-amine (**111a**) (97 mg, 0.5 mmol), 2-bromophenylacetaldehyde (**110**) (100 mg, 0.5 mmol) and *tert*-butyl isocianide (**4a**) (42 mg, 0.5 mmol). The reaction mixture was stirred at rt for 24 h in a sealed screw cap vial. The resulting mixture was concentrated and subjected to the column chromatography on silicagel with heptane-EtOAc (10%) as eluent to give the desired propargylamide **102m**. Yield: 161 mg, 56%. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.50-7.02 (m, 12H), 6.90 (bs, 2H), 4.74 (dd, J = 2.9, 8.9 Hz, 1H), 4.15-3.69 (m, 1H), 3.68-3.33 (m, 1H), 1.92 (bs, 6H), 1.37 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 173.6, 137.8, 134.4, 133.3, 132.7, 132.1, 129.6, 128.5, 128.4, 128.2, 127.4, 126.1, 125.1, 121.0, 92.8, 86.0, 65.0, 56.3, 51.4, 35.8, 30.3, 30.0, 28.8; HRMS (EI, $[M]^+$) for $C_{31}H_{32}BrClN_2O_2^{\bullet+}$ calcd. 578.1330, found 578.1321.

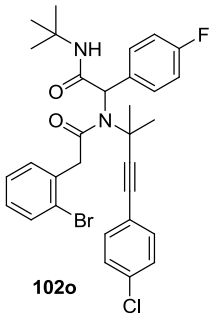
Synthesis of 2-(2-(2-bromophenyl)-*N*-(3-phenylprop-2-ynyl)acetamido)-*N*-*tert*-butylpentan-amide (102n) through the Ugi reaction



102n

2-Bromophenylacetic acid (**112**) (108 mg, 0.5 mmol) was dissolved in methanol (2 mL) followed by addition of 3-phenylpropargylamine (**111b**) (66 mg, 0.5 mmol), butyraldehyde (**2b**) (36 mg, 0.5 mmol) and *tert*-butyl isocianide (**4a**) (42 mg, 0.5 mmol). The reaction mixture was stirred at rt for 24 h in a sealed screw cap vial. The resulting mixture was concentrated and subjected to the column chromatography on silicagel with heptane-EtOAc (10%) as eluent. The fractions containing **102n** (determined by MS) were evaporated and transferred to the next reductive Heck cyclization step. Crude yield: 125 mg, 52%. HRMS (EI, $[M]^+$) for $C_{26}H_{31}BrN_2O_2^{\bullet+}$ calcd. 482.1563, found 482.1568.

Synthesis of 2-(2-bromophenyl)-*N*-(2-(*tert*-butylamino)-1-(4-fluorophenyl)-2-oxoethyl)-*N*-(3-(4-chlorophenyl)prop-2-ynyl)acetamide (102o) through the Ugi reaction

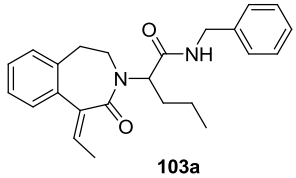


102o

2-Bromophenylacetic acid (**112**) (108 mg, 0.5 mmol) was dissolved in methanol (2 mL) followed by addition of 4-(4-chlorophenyl)-2-methylbut-3-yn-2-amine (**111a**) (97 mg, 0.5 mmol), 4-fluoro-benzaldehyde (**2g**) (62 mg, 0.5 mmol) and *tert*-butyl isocianide (**4a**) (42 mg, 0.5 mmol). The reaction mixture was stirred at rt for 24 h in a sealed screw cap vial. The resulting mixture was concentrated and subjected to the column chromatography on silicagel with heptane-EtOAc (10%) as eluent to give the desired propargylamide **102o**. Yield: 99 mg, 33%. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.63-6.90 (m, 12H), 5.95 (bs, 1H), 5.56 (bs, 1H), 4.33-3.45 (m, 2H), 2.00 (s, 3H), 1.88 (s, 3H), 1.31 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 172.5, 168.5, 162.1 (d, J = 247.5 Hz), 135.7, 134.7, 132.7, 132.5, 131.2, 130.1 (d, J = 7.9 Hz), 128.6, 128.4, 127.4, 125.1, 120.6, 115.6 (d, J = 21.5 Hz), 93.5, 84.6, 65.6, 57.0, 51.7, 44.5, 30.0, 29.5, 28.5; HRMS (EI, $[M]^+$) for $C_{31}H_{31}BrClFN_2O_2^{\bullet+}$ calcd. 596.1236, found 596.1270.

General procedure for the reductive Heck cyclization of propargylamides 102 into benzazepines 103-106

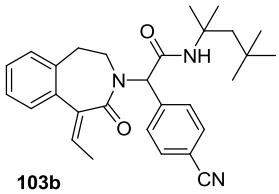
Propargylamide **102** (0.3 mmol) was placed into microwave vial and dissolved in DMF (3.3 mL) followed by addition of $Pd(PPh_3)_4$ (10.4 mg, 0.009 mmol), HCOONa (30.6 mg, 0.45 mmol) and distilled water (1.1 mL). The vial was several times evacuated and backfilled with argon. When the reaction vial was sealed and irradiated under stirring at the set temperature of 110 °C for 15 min utilizing maximum power of 100 W. Upon completion of the reaction the vial was cooled with a stream of air. The reaction mixture was diluted with EtOAc (50 mL), washed with water (2×50 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was subjected to column chromatography on silica gel with heptane–EtOAc (7-50%) as eluent.



103a

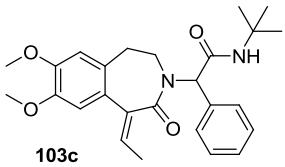
(*Z*)-*N*-benzyl-2-(1-ethylidene-2-oxo-4,5-dihydro-1*H*-benzo[*d*]azepin-3(2*H*)-yl)pentanamide (103a). Yield: 102 mg, 90%. Yellow solid; m.p. 109-111°C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.33-7.05 (m, 8H), 7.04-6.88 (m, 2H), 5.91 (q, J = 7.0 Hz, 1H), 5.05 (t, J = 7.7 Hz, 1H), 4.46 (dd, J = 6.4, 14.9 Hz, 1H), 4.26 (dd, J = 5.2, 14.9 Hz, 1H), 3.96-3.60 (m, 2H), 3.11-2.82 (m, 2H), 2.07-1.89 (m, 1H), 1.88-1.63 (m, 4H), 1.43-1.18 (m, 2H), 0.95 (t, J = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.8, 170.7, 139.5, 138.0, 134.8, 130.9, 130.1, 129.6, 128.5, 127.7, 127.2, 126.5, 55.2, 43.2, 41.0, 33.5, 30.2, 19.2, 15.5, 13.9; IR (ATR): v = 3284, 2958, 1633, 1527, 1456, 1414, 1228,

1169, 917, 745, 698, 609, 434; HRMS (EI, $[M]^+$) for $C_{24}H_{28}N_2O_2^{\bullet+}$ calcd. 376.2145, found 376.2135.



103b

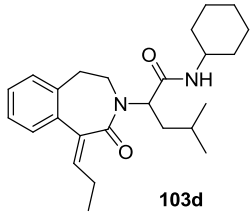
(*Z*)-2-(4-cyanophenyl)-2-(1-ethylidene-2-oxo-4,5-dihydro-1*H*-benzo[*d*]azepin-3(2*H*)-yl)-*N*-(2,4,4-trimethylpentan-2-yl)acetamide (103b). Yield: 108 mg, 79%. Yellow solid; m.p. 197-200°C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.61 (d, J = 8.1 Hz, 2H), 7.50 (d, J = 8.1 Hz, 2H), 7.25-7.12 (m, 3H), 7.05-6.91 (m, 1H), 6.44 (bs, 1H), 6.32 (s, 1H), 5.99 (q, J = 7.0 Hz, 1H), 3.96-3.68 (m, 2H), 3.15-2.88 (m, 1H), 2.68-2.38 (m, 1H), 1.89 (d, J = 7.0 Hz, 3H), 1.80 (d, J = 14.9 Hz, 1H), 1.63 (d, J = 14.9 Hz, 1H), 1.39 (s, 3H), 1.37 (s, 3H), 0.89 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.7, 167.4, 141.2, 139.1, 134.9, 134.6, 132.4, 131.6, 130.0, 129.7, 129.5, 127.9, 126.6, 118.4, 112.1, 59.2, 55.8, 51.6, 42.9, 33.3, 31.6, 31.4, 28.83, 28.76, 15.7; IR (ATR): v = 3305, 2923, 1686, 1617, 1556, 1471, 1362, 1170, 738, 559; HRMS (EI, $[M]^+$) for $C_{29}H_{35}N_3O_2^{\bullet+}$ calcd. 457.2724, found 457.2731.



103c

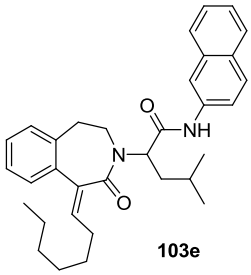
(*Z*)-*N*-*tert*-butyl-2-(1-ethylidene-7,8-dimethoxy-2-oxo-4,5-dihydro-1*H*-benzo[*d*]azepin-3(2*H*)-yl)-2-phenylacetamide (103c). Scale: 0.45 mmol. The material obtained after column chromatography was additionally purified by washing with diethyl ether. Yield: 149 mg,

76%. Pale yellow solid; m.p. 194-197°C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.52-7.31 (m, 5H), 6.74 (s, 1H), 6.41 (s, 1H), 6.19 (s, 1H), 5.94 (q, J = 7.0 Hz, 1H), 5.80 (bs, 1H), 3.92-3.74 (m, 7H), 3.74-3.60 (m, 1H), 3.03-2.71 (m, 1H), 2.51-2.22 (m, 1H), 1.94 (d, J = 7 Hz, 3H), 1.36 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.7, 168.7, 148.6, 147.3, 139.3, 135.8, 130.2, 129.1, 128.8, 128.3, 127.5, 127.1, 112.4, 59.8, 55.9, 55.8, 51.7, 42.7, 33.1, 28.6, 15.6; IR (ATR): ν = 3298, 2929, 1681, 1621, 1539, 1503, 1458, 1258, 1220, 1026, 925, 708, 565; HRMS (EI, $[M]^+$) for $C_{26}H_{32}N_2O_4^{\bullet+}$ calcd. 436.2357, found 436.2362.



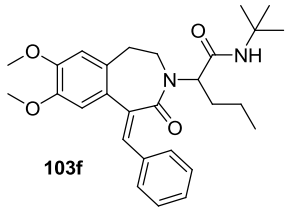
103d

(*Z*)-*N*-cyclohexyl-4-methyl-2-(2-oxo-1-propylidene-4,5-dihydro-1*H*-benzo[*d*]azepin-3(2*H*)-yl)pentanamide (103d). Yield: 92 mg, 77%. Yellow amorphous solid; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.33-7.11 (m, 3H), 7.10-6.98 (m, 1H), 6.21 (bd, J = 7.8 Hz, 1H), 5.87 (t, J = 7.6 Hz, 1H), 5.07 (t, J = 7.7 Hz, 1H), 3.93-3.57 (m, 3H), 3.21-2.87 (m, 2H), 2.28 (pentet, J = 7.5 Hz, 2H), 1.93-0.76 (m, 22H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.9, 169.9, 138.3, 137.5, 134.9, 134.8, 129.9, 129.7, 127.8, 126.5, 53.7, 47.9, 41.0, 36.5, 33.5, 32.7, 32.4, 25.4, 24.9, 24.6, 24.5, 23.3, 23.0, 22.3, 13.8; IR (ATR): ν = 3299, 2925, 2853, 1668, 1619, 1543, 1466, 893, 764, 735, 449; HRMS (EI, $[M]^+$) for $C_{25}H_{36}N_2O_2^{\bullet+}$ calcd. 396.2771, found 396.2785.



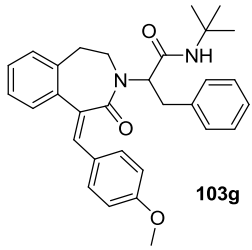
103e

(*Z*)-2-(1-heptylidene-2-oxo-4,5-dihydro-1*H*-benzo[*d*]azepin-3(2*H*)-yl)-4-methyl-*N*-(naphthalen-2-yl)pentanamide (103e). Scale: 0.2 mmol. Yield: 80 mg, 81%. Brownish solid; m.p. 173-175°C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.02 (d, J = 3.2 Hz, 1H), 8.18 (s, 1H), 7.82-7.61 (m, 3H), 7.50-7.30 (m, 3H), 7.28-7.09 (m, 3H), 7.07-6.93 (m, 1H), 5.89 (t, J = 7.6 Hz, 1H), 5.38 (t, J = 7.4 Hz, 1H), 3.97-3.73 (m, 2H), 3.21-2.94 (m, 2H), 2.27 (q, J = 7.4 Hz, 2H), 2.07-1.91 (m, 1H), 1.85-1.69 (m, 1H), 1.69-1.51 (m, 1H), 1.47-1.30 (m, 2H), 1.28-1.07 (m, 5H), 1.05-0.71 (m, 10H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 172.4, 169.4, 138.4, 137.4, 135.5, 134.84, 134.79, 133.8, 130.6, 130.1, 129.8, 128.6, 127.9, 127.7, 127.5, 126.7, 126.4, 124.9, 120.1, 116.7, 54.9, 41.3, 36.9, 33.7, 31.6, 30.2, 29.3, 29.2, 25.0, 22.9, 22.64, 22.57, 14.0; IR (ATR): v = 3264, 2922, 2853, 1690, 1609, 1555, 1469, 1416, 1351, 1221, 1183, 810, 742, 472; HRMS (EI, $[M]^+$) for $C_{33}H_{40}N_2O_2^{\bullet+}$ calcd. 496.3084, found 496.3098.



103f

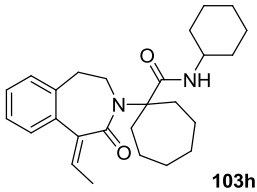
(*Z*)-2-(1-benzylidene-7,8-dimethoxy-2-oxo-4,5-dihydro-1*H*-benzo[*d*]azepin-3(2*H*)-yl)-*N*-*tert*-butylpentanamide (103f). Scale: 0.4 mmol. Yield: 162 mg, 87%. Pale yellow amorphous solid; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.54-7.44 (m, 2H), 7.38-7.22 (m, 3H), 6.92 (s, 1H), 6.65 (s, 1H), 6.56 (s, 1H), 6.16 (bs, 1H), 4.93 (t, J = 7.6 Hz, 1H), 4.12-3.65 (m, 8H), 3.25-2.78 (m, 2H), 2.10-1.61 (m, 2H), 1.40-1.23 (m, 2H), 1.18 (bs, 9H), 0.96 (t, J = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 172.0, 169.9, 149.1, 147.6, 138.2, 135.4, 130.9, 128.5, 128.4, 128.1, 127.7, 127.5, 112.5, 112.1, 56.00, 55.96, 55.5, 51.1, 41.0, 32.6, 29.7, 28.4, 19.1, 13.9; IR (ATR): ν = 3316, 2961, 1682, 1621, 1514, 1457, 1352, 1256, 1209, 1130, 1022, 859, 750, 694, 518; HRMS (EI, $[M]^+$) for $C_{28}H_{36}N_2O_4^{\bullet+}$ calcd. 464.2670, found 464.2667.



103g

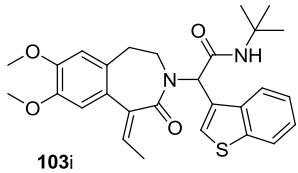
(*Z*)-*N*-*tert*-butyl-2-(1-(4-methoxybenzylidene)-2-oxo-4,5-dihydro-1*H*-benzo[*d*]azepin-3(2*H*)-yl)-3-phenylpropanamide (103g). Scale: 0.15 mmol. The material obtained after column chromatography was additionally purified by washing with diethyl ether. Yield: 45.6 mg, 63%. Pale yellow solid; m.p. 210-213°C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.45-7.33 (m, 1H), 7.33-7.09 (m, 9H), 7.09-6.97 (m, 1H), 6.74 (d, J

= 8.1 Hz, 2H), 6.57 (s, 1H), 6.13 (bs, 1H), 5.29-5.10 (m, 1H), 4.19-3.66 (m, 5H), 3.46-2.80 (m, 4H), 1.12 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 172.4, 169.5, 159.4, 137.1, 135.7, 135.5, 135.2, 132.0, 130.2, 129.9, 129.5, 129.1, 128.6, 128.0, 126.7, 114.0, 57.8, 55.2, 51.1, 41.7, 33.8, 32.6, 28.2; IR (ATR): v = 3351, 2962, 1676, 1618, 1510, 1413, 1250, 1175, 1034, 825, 742, 697, 543; HRMS (EI, $[M]^+$) for $C_{31}H_{34}N_2O_3^{\bullet+}$ calcd. 482.2564, found 482.2534.



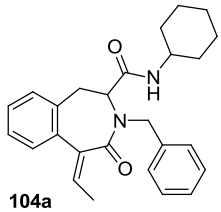
103h

(*Z*)-*N*-cyclohexyl-1-(1-ethylidene-2-oxo-4,5-dihydro-1*H*-benzo[*d*]azepin-3(2*H*)-yl)cycloheptanecarboxamide (103h). Scale: 0.15 mmol. Yield: 34.4 mg, 56%. Pale yellow solid; m.p. 152-154°C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.26-7.15 (m, 3H), 7.15-7.07 (m, 1H), 5.87 (q, J = 7.0 Hz, 1H), 5.62 (bd, J = 7.8 Hz, 1H), 4.04-3.80 (m, 2H), 3.75-3.50 (m, 1H), 3.31-3.09 (m, 2H), 2.57-2.32 (m, 2H), 2.06-1.98 (m, 2H), 1.89 (d, J = 7.0 Hz, 3H), 1.84-0.71 (m, 18H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 174.0, 171.6, 140.8, 135.4, 134.1, 129.98, 129.95, 129.6, 127.8, 126.8, 69.0, 47.8, 42.1, 35.9, 34.4, 32.5, 30.2, 25.6, 24.4, 23.9, 15.5; IR (ATR): v = 3372, 2923, 1679, 1641, 1521, 1405, 1194, 735, 617; HRMS (EI, $[M]^+$) for $C_{26}H_{36}N_2O_2^{\bullet+}$ calcd. 408.2771, found 408.2777.



103i

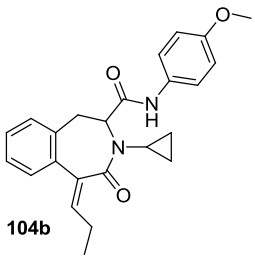
(*Z*)-2-(benzo[*b*]thiophen-3-yl)-*N*-*tert*-butyl-2-(1-ethylidene-7,8-dimethoxy-2-oxo-4,5-dihydro-1*H*-benzo[*d*]azepin-3(2*H*)-yl)acetamide (103i). Scale: 0.2 mmol. Yield: 78 mg, 79%. White solid; m.p. 244-246°C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.05 (s, 1H), 7.92-7.82 (m, 1H), 7.72-7.60 (m, 1H), 7.40-7.16 (m, 2H), 6.72 (s, 1H), 6.52 (s, 1H), 6.23 (bs, 1H), 6.08 (bs, 1H), 5.94 (q, J = 7.0 Hz, 1H), 3.87 (s, 3H), 3.81-3.60 (m, 5H), 3.06-2.63 (m, 1H), 2.38-2.03 (m, 1H), 1.97 (d, J = 7.0 Hz, 3H), 1.34 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.6, 168.4, 148.5, 147.2, 139.6, 139.1, 138.3, 130.0, 129.5, 127.9, 127.3, 126.8, 124.9, 124.5, 122.7, 121.7, 112.4, 112.2, 55.85, 55.79, 53.5, 51.6, 42.0, 32.7, 28.5, 15.5; IR (ATR): v = 3357, 2965, 1683, 1642, 1516, 1458, 1353, 1254, 1024, 845, 767, 573, 494, 431; HRMS (EI, $[M]^+$) for $C_{28}H_{32}N_2O_4S^{\bullet+}$ calcd. 492.2077, found 492.2065.



104a

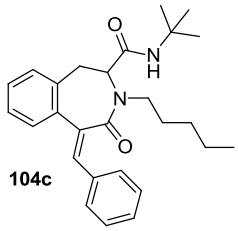
(*Z*)-3-benzyl-*N*-cyclohexyl-5-ethylidene-4-oxo-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine-2-carboxamide (104a). Scale: 0.2 mmol. Yield: 76.5 mg, 95%. Pale yellow amorphous solid; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.45-7.28 (m, 5H), 7.25-7.14 (m, 3H), 7.14-7.03 (m, 1H), 6.01 (q, J = 7.1 Hz, 1H), 5.14 (bd, J = 7.5 Hz, 1H), 4.73 (d, J = 14.6 Hz, 1H), 4.65 (d, J = 14.6 Hz, 1H), 4.13 (t, J = 4.4 Hz, 1H), 3.52-3.33

(m, 2H), 3.26 (dd, J = 4.0, 16.4 Hz, 1H), 2.03 (d, J = 7.1 Hz, 3H), 1.69-1.37 (m, 5H), 1.29-1.09 (m, 2H), 1.09-0.90 (m, 1H), 0.80-0.50 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 168.6, 168.2, 138.2, 137.2, 136.4, 133.9, 129.1, 128.7, 128.5, 128.03, 127.95, 127.1, 61.3, 50.7, 48.4, 33.7, 32.5, 32.4, 25.3, 24.7, 24.6, 16.8; IR (ATR): v = 3312, 2926, 2853, 1643, 1537, 1448, 1346, 1221, 729, 699, 453; HRMS (EI, $[M]^+$) for $C_{26}H_{30}N_2O_2^{\bullet+}$ calcd. 402.2302, found 402.2321.



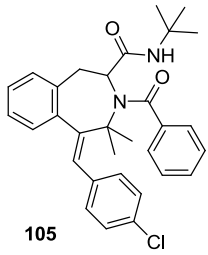
104b

(*Z*)-3-cyclopropyl-*N*-(4-methoxyphenyl)-4-oxo-5-propylidene-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine-2-carboxamide (104b). Yield: 90 mg, 77%. Brownish solid; m.p. 161-164°C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.40-7.30 (m, 1H), 7.29-7.10 (m, 6H), 6.80 (d, J = 8.8 Hz, 2H), 5.85 (t, J = 7.4 Hz, 1H), 4.36 (dd, J = 4.2, 6.0 Hz, 1H), 3.76 (s, 3H), 3.61 (dd, J = 6.0, 16.6 Hz, 1H), 3.31 (dd, J = 4.2, 16.6 Hz, 1H), 3.03-2.83 (m, 1H), 2.50-2.28 (m, 1H), 2.26-2.07 (m, 1H), 1.06-0.86 (m, 5H), 0.80-0.62 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.1, 167.9, 156.6, 143.1, 137.1, 136.2, 133.3, 130.2, 129.0, 128.8, 128.1, 127.3, 121.6, 114.2, 63.2, 55.5, 34.3, 31.5, 23.8, 13.7, 8.1, 7.9; IR (ATR): v = 3271, 2922, 1684, 1600, 1546, 1506, 1417, 1295, 1223, 1182, 1033, 835, 744, 714, 532; HRMS (EI, $[M]^+$) for $C_{24}H_{26}N_2O_3^{\bullet+}$ calcd. 390.1938, found 390.1952.



104c

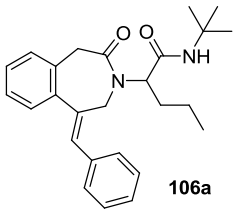
(*Z*)-5-benzylidene-*N*-*tert*-butyl-4-oxo-3-pentyl-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine-2-carboxamide (104c). Scale: 0.3 mmol. Yield: 111 mg, 88%. Yellow amorphous solid; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.64-7.51 (m, 2H), 7.44-7.12 (m, 7H), 6.61 (s, 1H), 5.57 (bs, 1H), 4.30-4.17 (m, 1H), 3.72-3.55 (m, 2H), 3.54-3.39 (m, 1H), 3.28 (dd, J = 4.0, 17.0 Hz, 1H), 1.81-1.54 (m, 2H), 1.47-1.27 (m, 4H), 1.00 (s, 9H), 0.91 (t, J = 6.7 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 169.9, 168.0, 137.4, 136.0, 135.4, 134.4, 129.7, 129.2, 128.8, 128.64, 128.61, 128.4, 127.2, 62.1, 51.4, 47.3, 33.7, 29.3, 28.1, 22.5, 14.1; IR (ATR): v = 3512, 3320, 2926, 1667, 1599, 1538, 1447, 1363, 1219, 754, 689, 499; HRMS (EI, $[M]^+$) for $C_{27}H_{34}N_2O_2^{\bullet+}$ calcd. 418.2615, found 418.2630.



105

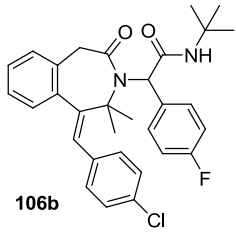
(*Z*)-3-benzoyl-*N*-*tert*-butyl-5-(4-chlorobenzylidene)-4,4-dimethyl-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine-2-carboxamide (105). Scale: 0.2 mmol. The material obtained after column chromatography was additionally purified by washing with diethyl ether. Yield: 49 mg, 49%. ^{1}H NMR (600 MHz, DMSO-d_6, 363 K): δ 7.42 (d, J = 8.3 Hz,

2H), 7.39-7.28 (m, 6H), 7.27-7.21 (m, 2H), 7.18-7.13 (m, 1H), 6.90-6.80 (m, 2H), 6.54 (s, 1H), 6.24 (bs, 1H), 4.45 (dd, J = 6.6, 11.7 Hz, 1H), 3.44 (dd, J = 11.7, 14.7 Hz, 1H), 3.23 (dd, J = 6.6, 14.7 Hz, 1H), 1.67 (s, 3H), 1.45 (s, 3H), 1.31 (s, 9H); ^{13}C NMR (150 MHz, DMSO-d_6, 363 K): δ 173.9, 169.7, 152.8, 144.7, 139.6, 137.8, 136.0, 132.2, 131.1, 130.7, 129.6, 129.2, 128.8, 128.3, 128.2, 127.8, 127.1, 126.8, 64.3, 62.3, 51.3, 35.0, 31.9, 29.4, 28.9; HRMS (EI, $[M]^+$) for $C_{31}H_{33}ClN_2O_2^{\bullet+}$ calcd. 500.2225, found 500.2225.



106a

(*Z*)-2-(1-benzylidene-4-oxo-4,5-dihydro-1*H*-benzo[*d*]azepin-3(2*H*)-yl)-*N*-*tert*-butylpentanamide (106a). Scale: 0.25 mmol. Yield: 24 mg, 24%. Yellow amorphous solid; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.70-7.59 (m, 1H), 7.48-7.38 (m, 2H), 7.38-7.21 (m, 6H), 6.95 (s, 1H), 5.55 (bs, 1H), 4.78-4.53 (m, 3H), 3.83 (s, 2H), 1.85-1.63 (m, 2H), 1.48-1.28 (m, 1H), 1.20-0.99 (m, 10H), 0.79 (t, J = 7.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 173.9, 169.6, 137.5, 136.4, 136.3, 133.2, 129.5, 129.1, 128.9, 128.8, 128.4, 128.0, 127.6, 127.3, 57.1, 51.1, 46.1, 43.4, 30.0, 28.5, 19.2, 13.8; IR (ATR): v = 3308, 2924, 1668, 1630, 1541, 1454, 1360, 1221, 750, 696, 562, 501; HRMS (EI, $[M]^+$) for $C_{26}H_{32}N_2O_2^{\bullet+}$ calcd. 404.2458, found 404.2475.



106b

(*Z*)-*N*-*tert*-butyl-2-(1-(4-chlorobenzylidene)-2,2-dimethyl-4-oxo-4,5-dihydro-1*H*-benzo[*d*]azepin-3(2*H*)-yl)-2-(4-fluorophenyl)acetamide (106b). Scale: 0.15 mmol. The material obtained after column chromatography was additionally purified by reversed phase preparative HPLC using gradient pump mode, MeCN/H_2O with 0.1% HCOOH (30-40-50-60-60-70-70-80-100%, 10 min intervals) as eluent and a flow rate of 10 mL/min. Yield: 24 mg, 31%. Yellow amorphous solid; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.44-7.22 (m, 6H), 7.18 (d, J = 8.0 Hz, 2H), 6.84-6.68 (m, 2H), 6.68-6.55 (m, 2H), 6.53 (s, 1H), 6.19 (bs, 1H), 4.71 (s, 1H), 4.15 (d, J = 13.2 Hz, 1H), 3.54 (d, J = 13.2 Hz, 1H), 1.53 (s, 3H), 1.43 (s, 3H), 1.24 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 174.0, 169.7, 161.7 (d, J = 246.4 Hz), 149.7, 142.2, 136.6, 135.5, 133.1, 133.0 (d, J = 3.7 Hz), 129.7, 129.1, 128.5, 128.4, 128.3, 128.1 (d, J = 4.1 Hz), 127.8, 126.4, 115.2 (d, J = 21.4 Hz), 65.2, 64.2, 51.1, 43.6, 30.0, 28.5; IR (ATR): v = 2922, 2852, 1682, 1641, 1507, 1223, 1155, 1091, 1012, 842, 793, 761, 583, 502, 457; HRMS (ESI, $[M+H]^+$) for $C_{31}H_{33}ClFN_2O_2^+$ calcd. 519.2209, found 519.2205.

4.11. Reductive Heck cyclization of propargylamides 102i' into benzazepines 103i

Propargylamide **102i'** (124 mg, 0.2 mmol) was placed into microwave vial and dissolved in DMF (2.25 mL) followed by addition of $Pd(PPh_3)_4$

(7 mg, 0.006 mmol), HCOONa (20.4 mg, 0.3 mmol) and distilled water (0.75 mL). The vial was several times evacuated and backfilled with argon. When the reaction vial was sealed and irradiated under stirring at the set temperature of 90 °C for 15 min utilizing maximum power of 100 W. Upon completion of the reaction the vial was cooled with a stream of air. The reaction mixture was diluted with EtOAc (40 mL), washed with water (2×40 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was subjected to column chromatography on silica gel with heptane–EtOAc (30-40%) as eluent to give pure **103i**. Yield: 90 mg, 91%.

Safety aspects

This section briefly outlines some guidelines and advices for the safe handling of materials and chemicals, when dealing with the protocols described in this thesis.

Before set up any experiment, it is highly recommended to go through the MSDS for all involved substances. In the current work, we have utilized a number of commercially available amines, aldehydes, organic acids, and isocyanides most of which are included in the KU Leuven Database of Hazardous Products that is another main source of information for the risk assessments.

Isocyanides are particularly toxic (by inhalation and in contact with scin). All syringes and laboratory glass exposed to isocyanides should be thoroughly washed in the fumehood and the generated wast should be appropriately treated and discarded. Volatile isocyanides have a very bad irritating smell.

It is also worth emphasizing that in case of inappropriate handling some commonly used solvents and materials may also possess underestimated danger to health. For example, chronic exposure to DCM is associated with a risk of cancer hazard. Long-term exposure (10 years or more) even to relatively low concentrations of silica dust may result in developing chronic silicosis.[77]

CV

Personal Information

Name	Anatoly A. Peshkov
Date of birth	April 2, 1990
Citizenship	Russia
E-mail	anatoly.peshkov@chem.kuleuven.be anatolypeshkov1990@gmail.com

Professional Career and Education

2012-2015 PhD at University of Leuven (KU Leuven), Belgium, Thesis title: "Synthesis and post-transformations of propiolic acid-derived Ugi adducts", Supervisor: Prof. Dr. Erik V. Van der Eycken.

2007-2012 Diploma in Chemical Engineering (Major: Technology of Inorganic Synthesis), D. Mendeleev University of Chemical Technology of Russia

Scholarships

2012-2015 Erasmus Mundus scholarship under the Triple I frame-work for the doctoral studies at the University of Leuven (KU Leuven), awarded on 5th April 2012

List of publications

1. Unexpected Regio- and Chemoselectivity of Cationic Gold-Catalyzed Cycloisomerizations of Propargylureas: Access to Tetrasubstituted 3,4-Dihydropyrimidin-2(1*H*)-ones
Olga P. Pereshivko, Vsevolod A. Peshkov, **Anatoly A. Peshkov**, Jeroen Jacobs, Luc Van Meervelt, Erik V. Van der Eycken, *Organic & Biomolecular Chemistry*, **2014**, *12*, 1741–1750.

2. Three-Component Reaction of a 2-Aminoazine, a 2-Oxoaldehyde and a Cyclic 1,3-Dicarbonyl Compound for the Synthesis of Imidazo[1,2-*a*]azine Derivatives
Vsevolod A. Peshkov, **Anatoly A. Peshkov**, Olga P. Pereshivko, Kristof Van Hecke, Lali L. Zamigaylo, Erik V. Van der Eycken, Nikolay Yu. Gorobets, *ACS Combinatorial Science*, **2014**, *16*, 535–542.

3. Assembly of 1*H*-Pyrrol-2(5*H*)-one Core through a Novel Cascade Ugi Reaction / 5-*endo*-*dig* Carbocyclization / Retro-Claisen Fragmentation Process
Anatoly A. Peshkov, Vsevolod A. Peshkov, Zhenghua Li, Olga P. Pereshivko, Erik V. Van der Eycken, *European Journal of Organic Chemistry*, **2014**, 6390–6393.

4. Diversification of the 3-Benzazepine Scaffold Applying Ugi/Reductive Heck Sequence

Anatoly A. Peshkov, Vsevolod A. Peshkov, Olga P. Pereshivko, Erik V. Van der Eycken, *Tetrahedron*, **2015**, *71*, 3863–3871.

5. Post-Ugi Carbocyclization/Fragmentation Sequence for the Synthesis of 6,7-Dihydro-5*H*-pyrrolo[3,4-*b*]pyridin-5-ones
Tran Thi Thu Trang,[#] **Anatoly A. Peshkov**,[#] Jeroen Jacobs, Luc Van Meervelt, Vsevolod A. Peshkov, Erik V. Van der Eycken, *Tetrahedron Letters*, **2015**, *56*, 2882–2886. [#] denotes equal contribution

6. Gold and Silver Catalyzed 7-*endo*-*dig* Cyclizations for the Synthesis of Oxazepines
Anatoly A. Peshkov, Anton A. Nechaev, Olga P. Pereshivko, Jan L. Goeman, Johan Van der Eycken, Vsevolod A. Peshkov, Erik V. Van der Eycken, *European Journal of Organic Chemistry*, **2015**, 4190–4197.

7. Heck-Suzuki Tandem Reaction for the Synthesis of 3-Benzazepines
Anatoly A. Peshkov, Vsevolod A. Peshkov, Olga P. Pereshivko, Kristof Van Hecke, Rakesh Kumar, Erik V. Van der Eycken, *Journal of Organic Chemistry*, **2015**, *80*, 6598–6608.

References

[1] a) H. Bienaymé, C. Hulme, G. Oddon, P. Schmitt *Chem. Eur. J.* **2000**, *6*, 3321–3329; b) J. Zhu, H. Bienaymé *Multicomponent Reactions*, 1st ed.; Wiley-VCH: Weinheim, Germany, **2005**; c) B. U. W. Maes, R. V. A. Orru, E. Ruijter *Synthesis of Heterocycles via Multicomponent Reaction I & II*; Springer: Heidelberg, **2010**.

[2] a) I. Ugi, R. Meyr, U. Fetzer, C. Steinbrückner *Angew. Chem*. **1959**, *71*, 386; b) I. Ugi, C. Steinbrückner *Angew. Chem*. **1960**, *72*, 267–268.

[3] a) I. Ugi *Angew. Chem. Int. Ed. Engl.* **1962**, *1*, 8–21; b) A. Dömling, I. Ugi *Angew. Chem. Int. Ed.* **2000**, *39*, 3168–3210; c) I. Ugi, B. Werner, A. Dömling *Molecules* **2003**, *8*, 53-66.

[4] a) O. Mumm *Ber. Dtsch. Chem. Ges.* **1910**, *43*, 886–893; b) J. S. P. Schwarz *J. Org. Chem.* **1972**, *37*, 2906–2908; c) N. Chéron, R. Ramozzi, L. El Kaïm, L. Grimaud, P. Fleurat-Lessard *J. Org. Chem.* **2012**, *77*, 1361–1366.

[5] S. Gedey, J. Van der Eycken, F. Fülöp *Org. Lett.* **2002**, *4*, 1967–1969.

[6] H. Tye, M. Whittaker *Org. Biomol. Chem.* **2004**, *2*, 813–815.

[7] S. Beaumont, P. Retailleau, P. Dauban, R. H. Dodd *Eur. J. Org. Chem.* **2008**, 5162–5175.

[8] V. P. Mehta, S. G. Modha, E. Ruijter, K. Van Hecke, L. Van Meervelt, C. Pannecouque, J. Balzarini, R. V. A. Orru, E. Van der Eycken *J. Org. Chem.* **2011**, *76*, 2828–2839.

[9] L. Banfi, A. Basso, R. Riva *Top. Heterocycl. Chem.* **2010**, *23*, 1−39.

[10] U. K. Sharma, N. Sharma, D. D. Vachhani, E. V. Van der Eycken *Chem. Soc. Rev.* **2015**, *44*, 1836−1860.

[11]. L. Zhang, F. Zhao, M. Zheng, Y. Zhai, H. Liu *Chem. Commun*. **2013**, *49*, 2894–2896.

[12]. V. Tyagi, S. Khan, P. M. S. Chauhan *Tetrahedron Lett*. **2013**, *54*, 1279–1284.

[13] T. T. T. Trang, A. A. Peshkov, J. Jacobs, L. Van Meervelt, V. A. Peshkov, E. V. Van der Eycken *Tetrahedron Lett.* **2015**, *56*, 2882–2886.

[14] a) L. El Kaïm, L. Grimaud, S. Wagschal *J. Org. Chem.* **2010**, *75*, 5343–5346; b) L. El Kaïm, L. Grimaud, S. Wagschal *Org. Biomol. Chem.* **2013**, *11*, 6883–6885.

[15] L. A. Polindara-García, L. D. Miranda *Org. Lett.* **2012**, 14, 5408–5411.

[16] For a focused review on the application of arylglyoxals in heterocyclic chemistry, see: B. Eftekhari-Sis, M. Zirak, A. Akbari *Chem. Rev.* **2013**, *113*, 2958–3043.

[17] For recent examples on the application of arylglyoxals in Ugi-type processes, see: a) M. Ayaz, G. Martinez-Ariza, C. Hulme Synlett **2014**, *25*, 1680–1684; b) J. Azuaje, A. El Maatougui, X. García-Mera, E. Sotelo, *ACS Comb. Sci.* **2014**, *16*, 403–411; c) X.-H. Zeng, H.-M. Wang, Y.-M. Yan, L. Wu, M.-W. Ding, Tetrahedron **2014**, *70*, 3647–3652.

[18] For an alternative strategy towards pyrrolones of type **43** utilizing the Ugi reaction of isocyanides, phosphonoacetic acids, primary amines and glyoxals followed by Wittig reaction (Horner/Wadsworth/Emmons variant), see: B. Beck, A. Picard, E. Herdtweck, A. Dömling *Org. Lett.* **2004**, *6*, 39–42.

[19] A. A. Peshkov, V. A. Peshkov, Z. Li, O. P. Pereshivko, E. V. Van der Eycken *Eur. J. Org. Chem.* **2014**, 6390–6393.

[20] For selected reviews, see: a) H. Huang, Y. Zhou, H. Liu *Beilstein J. Org. Chem.* **2011**, *7*, 897–936; b) H. C. Shen *Tetrahedron* **2008**, *64*, 3885–3903; c) A. S. K. Hashmi, M. Rudolph *Chem. Commun.* **2011**, *47*, 6536–6544; d) A. S. K. Hashmi, M. Bührle *Aldrichimica Acta*, **2010**, *43*, 27–33; e) X. Zeng *Chem. Rev.* **2013**, *113*, 6864−6900; f) A. S. Dudnik, N. Chernyak, V. Gevorgyan *Aldrichimica Acta* **2010**, *43*, 37–46; g) S. F. Kirsch *Synthesis* **2008**, 3183–3204; h) R. A. Widenhoefer, F. Song in *Catalyzed Carbon-Heteroatom Bond Formation* (Ed.: A. K. Yudin), Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim, **2010**, pp. 437–461; i) R. A. Widenhoefer, F. Song in *Catalyzed Carbon-Heteroatom Bond Formation* (Ed.: A. K. Yudin), Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim, **2010**, pp. 463–492; j) P. Belmont in *Silver in Organic Chemistry* (Ed.: M. Harmata), John Wiley & Sons, Inc., Hoboken, **2010**, pp. 143–165.

[21] For representative examples, see: a) R. Kazem Shiroodi, C. Rivera Vera, A. S. Dudnik, V. Gevorgyan *Tetrahedron Lett.* **2015**, *56*, 3251–3254; b) A. S. K. Hashmi, T. Häffner, M. Rudolph, F. Rominger *Eur. J. Org. Chem.* **2011**, 667–671; c) J. P. Weyrauch, A. S. K. Hashmi, A. Schuster, T. Hengst, S. Schetter, A. Littmann, M. Rudolph, M. Hamzic, J. Visus, F. Rominger, W. Frey, J. W. Bats *Chem. Eur. J.* **2010**, *16*, 956–963; d) V. A. Peshkov, O. P. Pereshivko, S. Sharma, T. Meganathan, V. S. Parmar, D. S. Ermolat'ev, E. V Van der Eycken *J. Org. Chem.* **2011**, *76*, 5867–5872; e) O. P. Pereshivko, V. A. Peshkov, A. A. Peshkov, J. Jacobs, L. Van Meervelt, E. V. Van der Eycken *Org. Biomol. Chem.* **2014**, *12*, 1741–1750; f) N. Sakai, N. Uchida, T. Konakahara *Tetrahedron Lett.* **2008**, *49*, 3437–3440.

[22] For representative examples, see: a) A. S. K. Hashmi, M. Rudolph, J. Huck, W. Frey, J. W. Bats, M. Hamzic *Angew. Chem. Int. Ed.* **2009**, *48*, 5848–5852; b) Y. Zhou, E. Feng, G. Liu, D. Ye, J. Li, H. Jiang, H. Liu *J. Org. Chem.* **2009**, *74*, 7344–7348; c) F. Liu, Y. Yu, J. Zhang *Angew. Chem. Int. Ed.* **2009**, *48*, 5505–5508; d) C. Ferrer, C. H. M. Amijs, A. M. Echavarren *Chem. Eur. J.* **2007**, *13*, 1358–1373.

[23] a) C. Ferrer, A. M. Echavarren *Angew. Chem. Int. Ed.* **2006**, *45*, 1105–1109; b) A. S. K. Hashmi, W. Yang, F. Rominger *Adv. Synth. Catal.* **2012**, *354*, 1273–1279; c) M. Gruit, A. Pews-Davtyan, M. Beller *Org. Biomol. Chem.* **2011**, *9*, 1148–1159; d) M. Gruit, D. Michalik, A. Tillack, M. Beller *Angew. Chem. Int. Ed.* **2009**, *48*, 7212–7216; e) G. Cera, P. Crispino, M. Monari, M. Bandini *Chem. Commun.* **2011**, *47*, 7803–7805.

[24] S. G. Modha, A. Kumar, D. D. Vachhani, J. Jacobs, S. K. Sharma, V. S. Parmar, L. V. Meervelt, E. V. Van der Eycken *Angew. Chem. Int. Ed.* **2012**, *51*, 9572–9575.

[25] This terminology follows Baldwin's classification. For more details, see: a) J. E. Baldwin *J. Chem. Soc. Chem. Commun.* **1976**, 734–736; b) J. E. Baldwin, R. C. Thomas, L. I. Kruse, L. Silberman *J. Org. Chem.* **1977**, *42*, 3846–3852; c) K. Gilmore, I. V. Alabugin *Chem. Rev.* **2011**, *111*, 6513–6556; d) I. V. Alabugin, K. Gilmore, M. Manoharan *J. Am. Chem. Soc.* **2011**, *133*, 12608–12623.

[26] For an analogous approach that use propargylamines as a triple bond source, see: A. Kumar, D. D. Vachhani, S. G. Modha, S. K. Sharma, V. S. Parmar, E. V. Van der Eycken *Beilstein J. Org. Chem.* **2013**, *9*, 2097–2102.

[27] A. Kumar, D. D. Vachhani, S. G. Modha, S. K. Sharma, V. S. Parmar, E. V. Van der Eycken *Synthesis* **2013**, 2571–2582.

[28] A. Kumar, Z. Li, S. K. Sharma, V. S. Parmar, E. V. Van der Eycken *Chem. Commun.* **2013**, *49*, 6803–6805.

[29] S. G. Modha, A. Kumar, D. D. Vachhani, S. K. Sharma, V. S. Parmar, E. V. Van der Eycken *Chem. Commun.* **2012**, *48*, 10916–10918.

[30] Z. Li, A. Kumar, D. D. Vachhani, S. K. Sharma, V. S. Parmar, E. V. Van der Eycken *Eur. J. Org. Chem.* **2014**, 2084–2091.

[31] A. Kumar, Z. Li, S. K. Sharma, V. S. Parmar, E. V. Van der Eycken *Org. Lett.* **2013**, *15*, 1874–1877.

[32] P. A. Donets, K. Van Hecke, L. Van Meervelt, E. V. Van der Eycken *Org. Lett.* **2009**, *11*, 3618–3621.

[33] V. A. Peshkov, O. P. Pereshivko, E. V. Van der Eycken *Adv. Synth. Catal.* **2012**, *354*, 2841–2848.

[34] S. G. Modha, D. D. Vachhani, J. Jacobs, L. V. Meervelt, E. V. Van der Eycken *Chem. Commun.* **2012**, *48*, 6550–6552.

[35] Considering the known reactivity of hydroxyl nucleophiles in gold-catalyzed additions to C–C triple bonds, such an outcome is not completely surprising. For representative examples, see: a) M. Schuler, F. Silva, C. Bobbio, A. Tessier, V. Gouverneur *Angew. Chem. Int. Ed.* **2008**, *47*, 7927–7930; *Angew. Chem.* **2008**, *120*, 8045; b) R. Rüttinger, J. Leutzow, M. Wilsdorf, K. Wilckens, C. Czekelius *Org. Lett.* **2011**, *13*, 224–227; c) K. Wilckens, M. Uhlemann, C. Czekelius *Chem. Eur. J.* **2009**, *15*, 13323–13326; d) L.-P. Liu, G. B. Hammond *Org. Lett.* **2009**, *11*, 5090–5092; e) A. Aponick, C.-Y. Li, J. A. Palmes *Org. Lett.* **2009**, *11*, 121–124; f) Y. Zhang, J. J. Xue, Z. J. Xin, Z. X. Xie, Y. Li *Synlett* **2008**, 940–944; g) A. Zhdanko, M. E. Maier *Eur. J. Org. Chem.* **2014**, 3411–3422.

[36] A. A. Peshkov, A. A. Nechaev, O. P. Pereshivko, J. L. Goeman, J. Van der Eycken, V. A. Peshkov, E. V. Van der Eycken *Eur. J. Org. Chem.* **2015**, 4190–4197.

[37] In the course of this study a similar approach towards oxazocines was reported, see: S. S. Scully, S.-L. Zheng, B. K. Wagner, S. L. Schreiber *Org. Lett.* **2015**, *17*, 418–421.

[38] For another relevant process utilizing $PtCl_4$ catalyst for the synthesis of bicyclic acetals featuring either an oxazipine or an oxazocine moiety, see: A. Diéguez-Vázquez, C. C. Tzschucke, W. Y. Lam, S. V. Ley *Angew. Chem. Int. Ed.* **2008**, *47*, 209–212.

[39] V. Gracias, J. D. Moore and S. W. Djuric *Tetrahedron Lett.* **2004**, *45*, 417–420.

[40] Z. Xiang, T. Luo, K. Lu, J. Cui, X. Shi, R. Fathi, J. Chen, Z. Yang *Org. Lett.* **2004**, *6*, 3155–3158

[41] a) T. Kametani, K. Fukumoto *Heterocycles* **1975**, *3*, 931–1004; b) J. Weinstock, J. P. Hieble, J. W. Wilson *Drugs Future* **1985**, *10*, 645–696; c) M. Kawase, S. Saito, N. Motohashi *Int. J. Antimicrob. Ag.* **2000**, *14*, 193–201; d) P. A. Donets *PhD Dissertation*, University of Leuven (KU Leuven), **2011**; (e) V. A. Peshkov *PhD Dissertation*, University of Leuven (KU Leuven), **2013** and references cited herein.

[42] N. Gulavita, A. Hori, Y. Shimizu, P. Laszlo, J. Clardy *Tetrahedron Lett.* **1988**, *29*, 4381–4384.

[43] E. Valencia, A. J. Freyer, M. Shamma, V. Fajardo *Tetrahedron Lett.* **1984**, *25*, 599–602.

[44] a) W. W. Paudler, G. I. Kerley, J. McKay *J. Org. Chem.* **1963**, *28*, 2194–2197; b) R. G. Powell, D. Weisleder, C. R. Smith, I. A. Wolff *Tetrahedron Lett.* **1969**, 4081–4084; c) S. K. Arora, R. B. Bates, R. A.

Grady, G. Germain, J. P. DeClerc, R. G. Powell *J. Org. Chem.* **1976**, *41*, 551–554.

[45] For representative examples of aphanorphine synthesis, see: a) J. R. Fuchs, R. L. Funk *Org. Lett.* **2001**, *3*, 3923–3925; b) M. Katoh, H. Inoue, A. Suzuki, T. Honda *Synlett* **2005**, *18*, 2820–2822; c) R. S. Grainger, E. J. Welsh *Angew. Chem. Int. Ed.* **2007**, *46*, 5377–5380; d) M. Li, P. Zhou, H. F. Roth *Synthesis* **2007**, 55–60; e) Z. Ma, H. Zhai *Synlett* **2007**, 161–163; f) Z. Ma, H. Hu, W. Xiong, H. Zhai *Tetrahedron* **2007**, *63*, 7523–7531; g) D. N. Mai, B. R. Rosen, J. P. Wolfe *Org. Lett.* **2011**, *13*, 2932–2935; h) M. Medjahdi, J. C. González-Gómez, F. Foubelo, M. Yus *Eur. J. Org. Chem.* **2011**, 2230–2234.

[46] For representative examples of lennoxamine synthesis, see: a) S. Couty, C. Meyer, J. Cossy *Tetrahedron Lett.* **2006**, *47*, 767–769; b) T. Taniguchi, K. Iwasaki, M. Uchiyama, O. Tamura, H. Ishibashi *Org. Lett.* **2005**, *7*, 4389–4390; c) D. L. Comins, S. Schilling, Y. Zhang *Org. Lett.* **2005**, *7*, 95–98; d) N. Kise, S. Isemoto, T. Sakurai *J. Org. Chem.* **2011**, *76*, 9856–9860.

[47] For representative examples of cephalotaxine synthesis, see: a) W.-D. Z. Li, W.-G. Duo, C.-H. Zhuang *Org. Lett.* **2011**, *13*, 3538–3541; b) N. Isono, M. Mori *J. Org. Chem.* **1995**, *60*, 115–119; c) A. Hameed, A. J. Blake, C. J. Hayes *J. Org. Chem.* **2008**, *73*, 8045–8048.

[48] a) R. G. Powell, D. Weisleder, C. R. Smith Jr. *J. Pharm. Sci.* **1972**, *61*, 1227–1230; b) D. C. Zhou, R. Zittoun, J. P. Marie *Bull. Cancer.* **1995**, *82*, 987–995.

[49] a) J. M. Whaun, N. D. Brown *Ann. Trop. Med. Parasit.* **1990**, *84*, 229–237; b) R M. Ekong, G. C. Kirby, G. Patel, J. D. Phillipson, D. C. Warhurst *Biochem. Pharmacol.* **1990**, *40*, 297–301.

[50] a) D. L. Ladd, J. Weinstock, M. Wise, G. W. Gessner, J. L. Sawyer, K. E. Flaim *J. Med. Chem.* **1986**, *29*, 1904–1912; b) J. Weinstock, D. L. Ladd, J. W. Wilson, C. K. Brush, N. C. F. Yim, G. Galladher, M. E. McCarthy, J. Silvestry, H. M. Sarau, K. E. Flaim, D. M. Ackerman, P. E. Setler, A. J. Tobia, R. A. Hahn *J. Med. Chem.* **1986**, *29*, 2315–2325; c) L. M. Brenner US Patent 4328153, **1982**.

[51] M. B. Murphy, C. Murray, G. D. Shorten *N. Engl. J. Med.* **2001**, 345, 1548–1557 and references cited herein.

[52] a) B. M. Smith, J. M. Smith, J. H. Tsai, J. A. Schultz, C. A. Gilson, S. A. Estrada, R. R. Chen, D. M. Park, E. B. Prieto, C. S. Gallardo, D. Sengupta, W. J. Thomsen, H. R. Saldana, K. T. Whelan, F. Menzaghi, R. R. Webb, N. R. A. Beeley *Bioorg. Med. Chem. Lett.* **2005**, *15*, 1467–1470; b) B. M. Smith, J. M. Smith, J. H. Tsai, J. A. Schultz, C. A. Gilson, S. A. Estrada, R. R. Chen, D. M. Park, E. B. Prieto, C. S. Gallardo, D. Sengupta, P. I. Dosa, J. A. Covel, A. Ren, R. R. Webb, N. R. A. Beeley, M. Martin, M. Morgan, S. Espitia, H. R. Saldana, C. Bjenning, K. T. Whelan, A. J. Grottick, F. Menzaghi, W. J. Thomsen *J. Med. Chem.* **2008**, *51*, 305–313.

[53] a) W. J. Thomsen, A. J. Grottick, F. Menzaghi, H. Reyes-Saldana, S. Espitia, D. Yuskin, K. Whelan, M. Martin, M. Morgan, W. Chen, H. Al-Shamma, B. Smith, D. Chalmers, D. Behan *J. Pharmacol. Exp. Ther.* **2008**, *325*, 577–587; b) S. R. Smith, W. A. Prosser, D. J. Donahue, M. E. Morgan, C. M. Anderson, W. R. Shanahan *Obesity* **2009**, *17*, 494–503.

[54] a) J. R. Pfister *Heterocycles* **1986**, *24*, 2099–2103; b) M. Pauvert, S. Collet, A. Guingan *Tetrahedron Lett.* **2003**, *44*, 4203–4206; c) A. T. Soldatenkov, S. A. Soldatova, J. A. Mamyrbekova-Bekro, G. S. Gimranova, A. V. Malkova, K. B. Polyanskii, N. M. Kolyadina, V. N. Khrus-

talev *Chem. Heterocycl. Comp.* **2012**, *48*, 1332–1339; d) T. Soeta, T. Ohgai, T. Sakai, S. Fujinami, Y. Ukaji *Org. Lett.* **2014**, *16*, 4854–4857; e) T. Xiao, L. Li, G. Lin, Z.-w. Mao, L. Zhou *Org. Lett.* **2014**, *16*, 4232–4235 f) Y.-M. Zhao, P. Gu, Y.-Q. Tu, H.-J. Zhang, Q.-W. Zhang, C.-A. Fan *J. Org. Chem.* **2010**, *75*, 5289–5295.

[55] J.-A. García-López, I. Saura-Llamas, J. E. McGrady, D. Bautista, J. Vicente *Organometallics* **2012**, *31*, 8333−8347.

[56] a) O. Krull, B. Wünsch *Bioorg. Med. Chem.* **2004**, *12*, 1439–1451; b) U. Wirt, R. Fröhlich, B. Wünsch *Tetrahedron: Asymmetry* **2005**, *16*, 2199–2202; c) U. Wirt, D. Schepmann, B. Wünsch *Eur. J. Org. Chem.* **2007**, 462–475; d) S. M. Husain, R. Fröhlich, D. Schepmann, B. Wünsch *J. Org. Chem.* **2009**, *74*, 2788–2793.

[57] a) Y. Yu, G. A. Stephenson, D. Mitchell *Tetrahedron Lett.* **2006**, *47*, 3811–3814; b) L. Zhang, D. Ye, Y. Zhou, G. Liu, E. Feng, H. Jiang, H. Liu *J. Org. Chem.* **2010**, *75*, 3671–3677.

[58] a) J. Fidalgo, L. Castedo, D. Dominguez *Heterocycles* **1994**, *39*, 581–589; b) T. Kaoudi, B. Quiclet-Sire, S. Seguin, S. Z. Zard *Angew. Chem. Int. Ed.* **2000**, *39*, 731–733.

[59] a) J. Weinstock, D. L. Ladd, J. W. Wilson, C. K. Brush, N. C. F. Yim, G. Galladher, M. E. McCarthy, J. Silvestry, H. M. Sarau, K. E. Flaim, D. M. Ackerman, P. E. Setler, A. J. Tobia, R. A. Hahn *J. Med. Chem.* **1986**, *29*, 2315–2325; b) B. M. Smith, J. M. Smith, J. H. Tsai, J. A. Schultz, C. A. Gilson, S. A. Estrada, R. R. Chen, D. M. Park, E. B. Prieto, C. S. Gallardo, D. Sengupta, W. J. Thomsen, H. R. Saldana, K. T. Whelan, F. Menzaghi, R. R. Webb, N. R. A. Beeley *Bioorg. Med. Chem. Lett.* **2005**, *15*, 1467–1470.

[60] L. F. Tietze, R. Schimpf *Synthesis* **1993**, 876–880.

[61] L. F. Tietze, R. Schimpf *Chem. Ber.* **1994**, *127*, 2235–2240.

[62] For the application of this methodology for the synthesis of other medium-ring containing systems, see: a) K. C. Majumdar, S. Chakravorty, T. Ghosh, B. Sridhar *Synlett* **2009**, 3127–3130; b) K. C. Majumdar, T. Ghosh, S. Chakravorty *Tetrahedron Lett.* **2010**, *51*, 3372–3375.

[63] For a general review featuring Pd-catalyzed formal hydroarylations of multiple bonds, see: S. Cacchi *Pure Appl. Chem.* **1990**, *62*, 713–722.

[64] For a general review on transition metal-catalyzed triple bond hydroarylations for the synthesis of heterocycles, see: Y. Yamamoto *Chem. Soc. Rev.* **2014**, *43*, 1575–1600.

[65] a) P. A. Donets, E. Van der Eycken *Org. Lett.* **2007**, *9*, 3017–3020; b) P. A. Donets, J. L. Goeman, J. Van der Eycken, K. Robeyns, L. Van Meervelt, E. Van der Eycken *Eur. J. Org. Chem.* **2009**, *6*, 793–796.

[66] For the application of this strategy for the synthesis of azocino[4,5,6-*cd*]indoles and azepino[5,4-*b*]indoles, see: V. A. Peshkov, S. Van Hove, P. A. Donets, O. P. Pereshivko, K. Van Hecke, L. Van Meervelt, E. V. Van der Eycken *Eur. J. Org. Chem.* **2011**, 1837–1840.

[67] For the modification of this strategy into a Heck-Suzuki tandem reaction, see: A. A. Peshkov, V. A. Peshkov, O. P. Pereshivko, K. Van Hecke, R. Kumar, E. V. Van der Eycken *J. Org. Chem.* **2015**, *80*, 6598–6608.

[68] For reviews on A^3-coupling, see: a) W.-J. Yoo, L. Zhao, C.-J. Li *Aldrichimica Acta* **2011**, *44*, 43–51; b) V. A. Peshkov, O. P. Pereshivko, E. V. Van der Eycken *Chem. Soc. Rev.* **2012**, *41*, 3790–3807.

[69] For selected recent applications of A^3-coupling in the synthesis of medium-sized rings, see: a) J. B. Bariwal, D. S. Ermolat'ev, T. N.

Glasnov, K. Van Hecke, V. P. Mehta, L. Van Meervelt, C. O. Kappe, E. V. Van der Eycken *Org. Lett.* **2010**, *12*, 2774–2777; b) N. Mont, V. P. Mehta, P. Appukkuttan, T. Beryozkina, S. Toppet, K. Van Hecke, L. Van Meervelt, A. Voet, M. DeMaeyer, E. V. Van der Eycken *J. Org. Chem.* **2008**, *73*, 7509–7516; c) G. Hooyberghs, H. De Coster, D. D. Vachhani, D. S. Ermolat'ev, E. V. Van der Eycken *Tetrahedron* **2013**, *69*, 4331–4337; d) G. Hooyberghs, S. Van Hove, J. Jacobs, L. Van Meervelt, E. V. Van der Eycken *Eur. J. Org. Chem.* **2015**, 4726–4731.

[70] V. A. Peshkov, O. P. Pereshivko, P. A. Donets, V. P. Mehta, E. V. Van der Eycken *Eur. J. Org. Chem.* **2010**, 4861–4867.

[71] For selected recent applications of the Ugi reaction for diversity-oriented synthesis of medium-ring containing systems, see: a) M. Sañudo, M. García-Valverde, S. Marcaccini, J. J. Delgado, J. Rojo, T. Torroba *J. Org. Chem.* **2009**, *74*, 2189–2192; b) D. D. Vachhani, A. Kumar, S. G. Modha, S. K. Sharma, V. S. Parmar, E. V. Van der Eycken *Eur. J. Org. Chem.* **2013**, 1223–1227; c) Z. Li, L. Legras, A. Kumar, D. D. Vachhani, S. K. Sharma, V. S. Parmar, E. V. Van der Eycken *Tetrahedron Lett.* **2014**, *55*, 2070–2074; d) L. Moni, L. Banfi, A. Basso, A. Brambilla, R. Riva *Beilstein J. Org. Chem.* **2014**, *10*, 209–212; e) J. Azuaje, J. M. Pérez-Rubio, V. Yaziji, A. El Maatougui, J. C. González-Gomez, V. M. Sánchez-Pedregal, A. Navarro-Vázquez, C. F. Masaguer, M. Teijeira, E. Sotelo *J. Org. Chem.* **2015**, *80*, 1533–1549.

[72] A. A. Peshkov, V. A. Peshkov, O. P. Pereshivko, E. V. Van der Eycken *Tetrahedron* **2015**, *71*, 3863–3871.

[73] For a recent study utilizing Ugi/Reductive Heck sequence for the diversity-oriented synthesis of intensively blue emissive 3-

hydroxyisoquinolines, see: L. Moni, M. Denißen, G. Valentini, T. J. J. Müller, R. Riva *Chem. Eur. J.* **2015**, *21*, 753–762.

[74] L. Banfi, R. Riva *Org. React.* **2005**, *65*, 1–140.

[75] The ratio was determined from ^{1}H NMR spectra.

[76] A. S. K. Hashmi, P. Haufe, A. R. Nass, J. W. Bats *Adv. Synth. Catal.* **2004**, *346*, 421−424.

[77] D. N. Weisman, D. E. Banks In *Interstitial Lung Disease* 4th ed. London, BC Decker Inc. **2003**.